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IMMUNE SERUM THERAPY FOR OROYA FEVER

CALDERON HOWE, M.D.

BOSTON

No specific treatment has as yet been developed for Oroya fever, the severe and often fatal anemic stage of Carrión's disease. There have been from time to time numerous attempts at immune therapy with serum or transfusions of whole blood from patients convalescing or recovered from various stages of Carrión's disease.[1] There have undoubtedly been many more trials at therapy along these lines than have been published. The few reports available, however, are inconclusive and neither substantiate nor detract from the possibility that such forms of passive immunization may be beneficial in certain cases.

In the field of chemotherapy, arsenical preparations have been tried by certain investigators [2]; but the evidence for any consistent success in this direction has been entirely unconvincing.

The present communication deals with 3 cases of Oroya fever in which hyperimmune rabbit serum containing a high titer of agglutinins for Bartonella bacilliformis was given in moderately large intravenous doses. The results obtained, though not entirely conclusive, are thought to be suggestive enough to warrant reporting.

MATERIALS AND METHODS

Production of Immune Serum.—In immunizing rabbits against B. bacilliformis, the organism responsible for Oroya fever, four strains were used. These originated from four different sources, as follows: The first strain was isolated from the proboscis of a Peruvian sandfly by Dr. Marshall Hertig in 1939. The second originated from a patient with Oroya fever in Peru and was obtained by Dr. Q. M. Geiman in 1939. The third strain was isolated from a patient with severe Oroya fever in Colombia in 1940 and was obtained from Dr. José Jiménez Franco, of Lima. The fourth strain, from a patient with severe Oroya fever in Peru, was isolated by me in 1940.

All of these strains had been maintained in the laboratory on Geiman blood agar and were consistently found to be motile. After five days' incubation at 28 C. the growth was washed off the slants with isotonic solution of sodium chloride, centrifuged and resuspended in isotonic solution of sodium chloride. The suspension used in immunizing rabbits consisted of a mixture of equal parts of all four strains, representing a concentration of the growth of two slants per cubic centimeter of suspending medium.

Nine rabbits received from seven to eleven inoculations, three inoculations of 1 cc. each being given on three successive days, with rest periods of three to four days between the series of three injections (table 1). The antigen was given intravenously. One animal (rabbit 1533) was immunized with a suspension of formaldehyde-treated organisms of the same basic composition as that given to the remaining animals in the fresh untreated state.

This investigation was financed in part from the Repayments Fund of the Department of Comparative Pathology and Tropical Medicine, Harvard Medical School.

From the Department of Comparative Pathology and Tropical Medicine, Harvard Medical School, and the National Institute of Hygiene and Public Health, Lima, Peru.

1. Odriozola, E.: Cong. méd. latino-am. **5**:139, 1913. Olaechea, A. S.: Rev. méd. peruana **4**:412, 1932. Groot, H.; Mayoral, P., and Martínez, R. E.: Rev. Fac. de med., Bogotá **9**:545, 1941.

2. Manrique, B.: Reforma med., Lima, 1937, vol. 23. de la Rocha, L. E.: Bol. Inf. de la Asoc. méd. per., 1938, vol. 5.

At the end of the total period of immunization, each animal was bled two, or in some instances three, times. The first two bleedings, of 50 cc. each, were carried out on the same day, and each was followed by the intravenous administration of 30 cc. of 20 per cent solution of dextrose. The third bleeding took place the following day if the animal was scheduled to be bled out for the maximum yield of serum.

Four of the rabbits in the present series (rabbits A, B, 1531 and 1533) had been used in earlier experiments involving immunization with the same four strains of B. bacilliformis previously described. The titer which had been obtained for each animal is shown in table 1. This titer, when it was high, had declined somewhat during the six months between the original immunization and that carried out for the present investigation. It is of interest to note that the 5 remaining rabbits (D, E, F, G and H), which had not been previously immunized, produced titers equal to those of the first group of animals.

The titer of the serum from these animals at the end of the period of immunization was consistently high, in most instances agglutination occurring at a final serum dilution, after the addition of the antigen, of 1:2,560. The serum from the 1 rabbit (rabbit 1533) immunized with suspension of formaldehyde-treated organisms agglutinated to a titer as high as did that from the animals immunized with the fresh untreated organisms.

In determining the agglutinating titer of these serums, the agglutination test was performed with a formaldehyde-treated antigen. This antigen consisted of a mixture of the four strains

TABLE 1.—*Immunization of Rabbits*

Rabbit Number	First Immunization Highest Agglutinin Titer Obtained	Second Immunization Number of Injections	Total Amount of Suspension Given, Cc.	Final Agglutinin Titer (Expressed as Final Dilution of Serum)		
				First Bleeding	Second Bleeding	Third Bleeding
A	1:10	7	14	1:2560		
B	1:160	11	18	1:2560	1:2560	
1531	1:320	11	18	1:640		
1533*	1:320	7	7.5	1:2560	1:2560	1:2560
D	No previous immunization	11	13	1:2560	1:2560	
E	No previous immunization	11	13	1:2560	1:2560	
F	No previous immunization	11	13	1:2560	1:2560	
G	No previous immunization	9	7.5	1:2560	1:2560	
H	No previous immunization	9	7.5	1:2560	1:2560	

* Immunized with a suspension of formaldehyde-treated organisms.

used in immunizing the animals suspended in a 0.4 per cent solution of formaldehyde U. S. P. in isotonic solution of sodium chloride. The type of flocculus occurring with this antigen when agglutinated with serum from rabbits immunized with live and with formaldehyde-treated organisms, was seen grossly to be fine and flaky. Under the dark field microscope, the organisms were found to be arranged in strands closely interwoven. This was in striking contrast to the appearance of the flocculus produced by agglutination of living organisms by hyperimmune rabbit serum.[3] Here the flocculus was tightly coherent and coarse, and under the dark field microscope the organisms were seen to be tightly clumped. Agglutination occurred at higher dilution of serum with the formaldehyde-treated antigen than with the fresh untreated antigen. The former seems thus to be more sensitive than the latter.

REPORT OF CASES

CASE 1.—A 51 year old foreman, in the employ of an electric power project in the Santa Eulalia valley, was seen at his home, in Lima, on April 12, 1942, complaining of fever, malaise and increasing prostration of eighteen days' duration and deep jaundice of seven days' duration.

History.—His past history revealed that he had had typhoid in 1900, gonorrhea in 1917 and 1929 and malaria in 1921. There was no history of addiction to alcohol. A native of Lima, his residence in regions where Carrión's disease is endemic had been prolonged but divided into three periods, as follows: 1928-1929, Autisha; 1934 to 1938, Callahuanca and Barbablanca; 1938 to 1942, Autisha. In the intervening periods, he had lived in Chosica, Huancavalica, Lima

3. Howe, C.: J. Exper. Med. **75**:65, 1942.

and Cuzco, in none of which localities Carrión's disease is known to occur. At no time had he had any severe illness, unexplained fever, jaundice or eruption of any kind. It was assumed, therefore, that, although he had had prolonged exposure in the endemic regions of the Santa Eulalia valley, he had never contracted clinical Carrión's disease in any form. He had been seen by me on March 10, 1942 in Autisha, at which time he was in good health. Cultures of blood taken on that date showed no growth of organisms; agglutination tests with B. bacilliformis gave negative reactions in all dilutions; the hemoglobin content was 11 Gm. per hundred cubic centimeters, and organisms were not seen in the blood film.

The patient had remained asymptomatic until March 25, when he was taken with a sudden chill, with malaise, and with sweating and a temperature of 104 F. For the ensuing eleven days, during the last nine of which he was in Lima, his temperature had been noted to be only slightly elevated. From April 5 to April 9, he had again been in Autisha. A blood count done on April 7 had shown the erythrocytes to number 4,600,000 per cubic millimeter and the leukocytes 7,000 per cubic millimeter with a normal differential count; B. bacilliformis had not been observed in a careful examination of the blood films.

On April 5, he had noted the sudden appearance of jaundice, which day by day increased in intensity. His urine had become coffee colored; the stools had remained normal in color, and

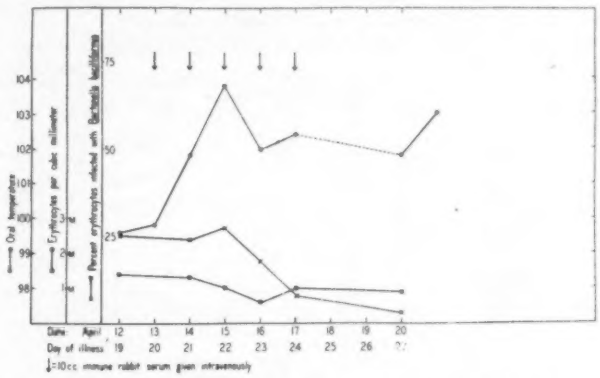

Fig. 1 (case 1).—Course of the disease in a case of treated Oroya fever.

TABLE 2.—*Laboratory Data in Case 1*

Date	Day of Disease	RBC	WBC	Hb., Gm.	RBC Infected, %	Hematocrit	Blood Cultures	Agglutination Test, Final Dilutions of Serum 1:2	1:10	1:20	1:40	1:80	1:160
March 10	..	.....	.....	11	0	..	—	0	0	0	–	–	–
April 7	14	4,600,000	7,000	....	0								
April 12	19	1,400,000	9,300	5.0	25	29	+	4	1	0	–	–	–
April 14	21	1,300,000	8,700	4.0	24	12	+	4	3	2	0	0	0
April 15	22	1,000,000	.....	3.5*	27	.	+	4	4	3	2	1	0
April 16	23	600,000	.....	3.5*	18	..	+						
April 17	24	1,000,000	.....	3.0*	8	.	+	4	4	3	3	2	0
April 20	27	900,000	5,900	3.5	3	12	+	4	4	3	2	1	0
June 6	47	.....	.....	....	..	.	+						

	Blood Chemistry, Gm. per 100 Cc.			Urinalysis		
	Total Protein	Albumin	Globulin	Protein	Urobilin	Sediment
April 17	6.6	2.9	3.7	Slight trace	4 plus	Not remarkable

* Determination obtained on electric photocolorimeter.

he had vomited two or three times a day during the ensuing week. On April 12 I saw him for the second time, in Lima, where he had been confined to bed for three days.

Physical Examination.—The only significant conditions observed on physical examination were a temperature of 104 F., severe jaundice, moderate dehydration, an enlarged liver (palpable 3 fingerbreadths below the right costal margin) and a moderately loud systolic murmur at the apex.

The laboratory data are summarized in table 2. It is noteworthy that in five days (April 7 to April 12) the red blood cell count had fallen to 1,400,000 per cubic millimeter and the hemoglobin content to 5 Gm. per hundred cubic centimeters and that on April 12 B. bacilliformis was seen for the first time, in 25 per cent of the erythrocytes.

Subsequent Course.—The patient's temperature remained elevated during the ensuing week (fig. 1), and he continued to complain of extreme malaise, anorexia, insomnia and occasional nausea and vomiting. The jaundice had diminished noticeably by the end of the week. The patient improved slowly, and he was reported on August 12 to be well on the way to recovery. No eruption had appeared up to that time.

Treatment.—During the acute stage of his illness, the patient was treated with parenteral injections of vitamin B complex and liver extract. He was also given a total of 50 cc. of

TABLE 3.—*Laboratory Data in Case 2*

Date	Day of Disease	RBC	WBC	Hb., Gm.	RBC Infected, %	Hematoerit	Blood Cultures	Agglutination Test, Final Dilutions of Serum					
								1:2	1:10	1:20	1:40	1:80	1:160
April 3	6	600,000	14,000	2.5	56	9	+	4	4	1	0	–	–
April 5	8	900,000	14,900	2.6	68								
April 7	10	900,000	12,400	3.5	20	11	+	4	4	2	0	–	–
April 8	11	1,200,000	9,700	4.0	16	12	+	4	4	4	–	–	–
April 9	12	900,000	7,800	3.8	4								
April 10	13	1,200,000	4,900	4.5*	1	26	+	4	4	4	–	–	–
April 11	14	1,400,000	6,800	4.3	0	17	+	4	4	4	3	0	–
April 12	15	1,800,000	10,800	–	—	..	..	–	–	–	–	–	–
April 13	16	1,900,000	12,000	5.3	0	20	+	4	4	4	–	–	–
April 14	17	1,400,000	7,300	4.3	0	18	+	4	4	4	2	1	0
April 15	18	1,500,000	.....	4.8	..	17	+	4	4	4	2	1	0
April 16	19	1,500,000	.....	5.5	..	..	..	4	4	4	3	2	0
April 20	23	1,700,000	10,500	5.5	..	22	+	4	4	3	2	1	
May 18	..	.....	.....	...	..	..	+						
June 5	..	3,600,000	9,800	...	..								

	Blood Chemistry, Gm. per 100 Cc.		
	Total Protein	Albumin	Globulin
April 20	6.0	3.4	2.6

* Determination obtained on electric photocolorimeter.

hyperimmune rabbit serum in intravenous doses of 10 cc. each on the twentieth through the twenty-fourth day of his illness (fig. 1). There was no untoward reaction, and an intradermal test before the administration of each dose invariably gave a negative result.

CASE 2.—A 15 year old native of the village of Vilcabama, in the Department of Apurimac, was seen in the Hospital Dos de Mayo in Lima on April 3, 1942, two days after his admission.

History.—The patient had lived in his native village, where no verruga is known to occur, until nine months prior to admission to the hospital, at which time he had gone to Cuzco. Here he had remained for six months; and he had then made his way to Lima via Ayacucho, Huancayo and the Rimac valley. The trip from Huancayo to Lima, including passage through the verruga zone, had been made in one day and one night. He had arrived in Lima for the first time three months prior to his admission to the hospital, his only exposure to infection up to that point having occurred during the night of travel, previously alluded to, through the lower Rimac valley. One month prior to admission, the patient had gone up the Rimac valley as far as Matucana, the upper limit of the verruga zone, stopping at different points on the way up and back seeking work. Eight days were spent in thus traversing the verruga zone, and the patient returned to Lima twenty-eight days prior to admission, on March 4. Three days prior to admission, on March 29, he was seized with a sudden chill, severe febrile symptoms, headache and extreme malaise. Three days later, on April 1, he was admitted to the hospital because of exhaustion and inability to work, with fever and extreme weakness.

Physical Examination.—Moderate icterus was evident. The mucous membranes were extremely pale, and the patient was perspiring profusely and complaining of shortness of breath. The lungs were clear to auscultation and were resonant throughout. Over the apex of the heart there was heard a moderately loud systolic murmur. The liver and spleen were not palpable. There were a few small cervical lymph nodes which were slightly enlarged and not tender. Physical examination yielded otherwise unremarkable results.

The laboratory data are summarized in table 3.

Subsequent Course.—The patient's course was at first only moderately febrile. Later, however, he had an irregular fever, the temperature ranging from 100 to 103 F. (fig. 2). At no time did he feel desperately ill. On the fourteenth day of his illness, he was discovered to have the beginning of a sudaminal eruption, characterized by pale nodules 1 to 2 mm. in diameter, which appeared first over the right wrist and lower part of the forearm. Within five or six days this eruption had spread over the chest and abdomen, and by the twenty-first day of the disease it had spread in miliary form over the entire trunk and over all four extremities. A specimen of the skin over the right wrist at the point where the eruption had first appeared was taken for biopsy, but nothing characteristic was seen on section of the specimen. About one month later, there was found at the site of the biopsy specimen a larger typical verruga nodule, about 1 cm. in diameter. On the thirtieth day of the disease, the verrucous eruption became secondarily infected, with the appearance of oozing impetiginous lesions over most of the body. As this superimposed infection subsided during the ensuing two

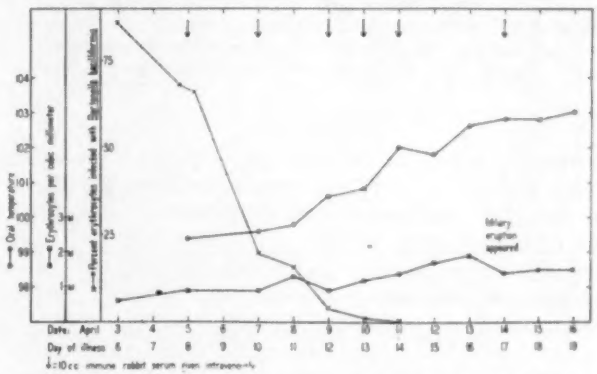

Fig. 2 (case 2).—Course of the disease in a case of treated Oroya fever.

weeks, the miliary verruga lesions again became visible as red spots on the skin. By about the seventh week of the disease, that is five weeks after the appearance of the verruga eruption, signs of eruption had almost completely subsided. The patient was reported to be in good health at that time. He was discharged from the hospital and has not been heard from since then; hence no long term follow-up has been possible.

Treatment.—Along with minimal nonspecific supportive therapy, this patient received a total of 60 cc. of hyperimmune rabbit serum (fig. 2). This was administered in intravenous doses of 10 cc. each on the eighth, tenth, twelfth, thirteenth, fourteenth and seventeenth days of the patient's illness. There were no untoward reactions, and an intradermal test before each dose of serum invariably gave a negative reaction.

Case 3.—A 21 year old member of a military detachment, a native of Ayacucho, was seen at the military hospital of San Bartolomé, in Lima, on April 13, 1942. His past history was unremarkable except for his having had typhus in childhood.

History.—The patient had completed a tour of duty at Chinchipe, on the Ecuadorian frontier, from July 1941 to Feb. 28, 1942. During the first week in March 1942, he had gone to Chanchaqui, between Piura and Huanaco, where verruga is not known to occur, and he had returned to Lima by March 6, 1942. On March 9, he had left Lima for Ayacucho and had been delayed between the hours of 4 and 8 p. m. on March 10, at Huanta, in the endemic region, by a landslide which had blocked the road. He had arrived in Ayacucho on March 11, had stayed there until March 24 and had returned to Lima on March 25. At noon on March 23 he had been taken with a sudden chill, complaining of headache, malaise, "fever" and

articular pains. The next morning he had vomited once. During the next few days, his symptoms had continued, with chilly sensations, irregular afternoon fever and ten to twelve diarrheic bowel movements without blood or mucus. He had been admitted to the hospital on March 25.

Physical Examination.—When seen for the first time by me, on April 13, the patient was extremely pale and weak, was sweating profusely and had pronounced edema of the face and of both lower eyelids. There was severe scleral icterus. He had had several profuse nosebleeds during the day, which had been arrested by tight packing of the anterior and posterior nasal passages. The temperature was 102.6 F., the pulse rate 108 and the respiratory rate 16. A few small cervical glands were palpable. The lungs were resonant and clear to auscultation throughout, and the heart was not remarkable. The liver and spleen were not made out, and there was no evidence of fluid in the abdomen. The physical examination otherwise revealed unremarkable conditions.

The laboratory data are summarized in table 4.

Subsequent Course.—The patient had a sustained fever during most of the short time (fig. 3) he was being followed by me. On the twenty-eighth day of his disease, his tempera-

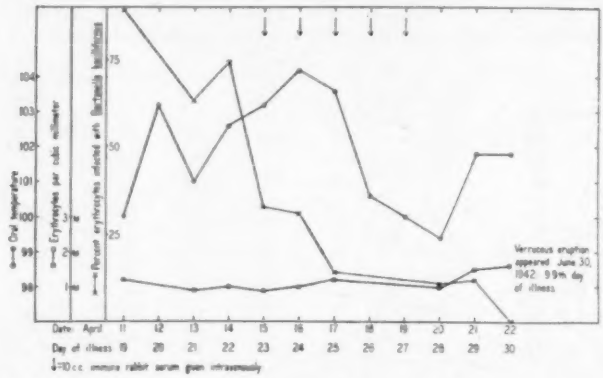
Oral temperature
Erythrocytes per cubic millimeter
Percent erythrocytes infected with Bartonella bacilliformis
Verrucous eruption appeared June 30, 1942, 9th day of illness
Date April
Day of illness
10 cc. immune rabbit serum given intravenously

Fig. 3 (case 3).—Course of the disease in a case of treated Oroya fever.

TABLE 4.—*Laboratory Data in Case 3*

Date	Day of Disease	RBC	WBC	Hb., Gm.	RBC Infected, %	Hematocrit	Blood Cultures	Agglutination Test, Final Dilutions of Serum 1:2	1:10	1:20	1:40	1:80	1:160
April 11	19	1,200,000	5,400	3.8	89	15							
April 13	21	900,000	13,200	3.3	63	10	+	3	1	0	-	-	-
April 14	22	1,000,000	10,200	2.8	74	12	+	4	2	0	0	0	0
April 15	23	900,000	.....	3.0	33	10	+	4	4	3	2	0	-
April 16	24	1,000,000	.....	2.7*	31	..	+						
April 17	25	1,200,000	.....	3.9	14	..	+	4	4	3	3	1	0
April 18	26	.....	.....	...	..	..	..	4	4	4	3	2	0
April 20	28	1,000,000	4,200	3.5	11	12	+	4	4	4	3	3	1
April 21	29	1,500,000	9,400	5.0	12								
April 22	30	1,600,000	14,600	...	0								
May 18	56	.....	.....	...	..	..	..	0	0	0	0	0	0

	Blood Chemistry						
	Serum Bilirubin, Mg. per 100 Cc.	Icteric Index	Total Protein, Gm. per 100 Cc.	Albumin, Gm. per 100 Cc.	Globulin, Gm. per 100 Cc.	Bleeding Time, Min.	Clotting Time, Min.
April 11	3	..	...	...	...	4	6
April 13	..	15	...				
April 14	..	12	...				
April 17	..	6	6.0	3.4	2.6		
April 21	..	4	...				

* Determination obtained on electric photocolorimeter.

ture was 99.4 F. On the twenty-fourth day, he was found to have pronounced and painful swelling of the neck at the angle of the jaw bilaterally, greater on the left than on the right. This condition was thought to represent an acute cervical adenitis. The patient's diarrhea continued intermittently, without blood or mucus. There was tenderness over the course of the large bowel, without any spasm of the abdominal wall. By the twenty-ninth day, the swelling in the neck had subsided and become less painful. The diarrhea was ascribed to a possible typhoid or paratyphoid infection, and the patient's serum was found to agglutinate Eberthella typhosa to a dilution of 1:500.

During the subsequent two months, the patient's condition was reported to have run a febrile course; he was said to have exhibited signs of what may have been mild peripheral neuritis, which subsequently subsided completely. His anemia improved gradually, with only minimal supportive therapy, and by mid-July his red blood cell count was reported to have reached 3,000,000, with no organisms having been seen on smear since April 22, the thirtieth day of his illness.

On June 30, the ninety-ninth day of his disease, a typical eruption, consisting of scattered pea-sized verrugas on the face and extremities, is reported to have developed. His general improvement was steady thereafter, and he left the hospital in August, about four months after the onset of his illness, still with definite eruption present.

Treatment.—On the twenty-first and twenty-sixth days of his illness, the patient received transfusions of whole blood, of 100 and 150 cc. respectively. This blood had been taken from donors who had denied having had Carrión's disease in the past. From the twenty-third to the twenty-seventh day inclusive, the patient received five daily intravenous doses, of 10 cc. each, of hyperimmune rabbit serum, without untoward reaction (fig. 3); an intradermal test prior to each dose invariably gave a negative reaction. Further supportive treatment was minimal.

DISCUSSION

In none of these 3 cases was the actual clinical picture dramatically altered by the administration of specific immune rabbit serum. The only point worth noting in this connection is the early appearance of the typical miliary eruption (on the fourteenth day of illness) in the second case, in which invasion of the blood stream was severe (fig. 1). The usual course of events in untreated severe Oroya fever is for the eruption to appear some weeks or months after the acute hemolytic infection of the blood stream has subsided. In this case, the eruption appeared shortly after the number of parasitized erythrocytes had been reduced below a level at which they were easily detectable by microscopic examination of the blood film, although cultures of the blood contained organisms for some time thereafter. The changes in the blood picture in these 3 cases were more striking.

In all 3 cases, measurable diminution in the percentage of infected erythrocytes began simultaneously with or shortly after the institution of serum treatment (figs. 1, 2 and 3). This reduction was real, not apparent, since the red blood cell count remained stationary or even rose slightly while the percentage of parasitized cells fell precipitously. Whether this change was pure coincidence or whether the immune serum administered was partially or wholly responsible for the rapid changes cannot be determined at present. There are two pieces of circumstantial evidence which lend support to the belief that this passive immunization may have hastened the process of reducing the degree of invasion of the blood stream.

The first of these lies in a comparison of the course of the disease in these cases with serum treatment with the natural course of events in cases of Oroya fever in which the patient survived wholly without treatment of any kind. In figure 4 are charted the percentages of infected erythrocytes determined on successive days for several patients from Colombia with Oroya fever. The gradual reduction in the number of B. bacilliformis organisms visible on direct smear of blood from these patients took place over a definitely longer period than in the cases herein

reported. It is not impossible that this difference may represent the favorable effect of passive immunization.

The second piece of evidence which suggests that immune serum has some effect on organisms circulating in the blood stream lies in certain changes noted in the appearance of the growth in cultures of blood taken on successive days, including those on which serum was administered. In all 3 cases, the colonies of organisms as seen in Geiman semisolid medium in the first blood culture taken before institution of therapy were finely granular and exceedingly numerous. As each dose of serum was given, colonies in serial blood cultures became strikingly different in appearance, those in the later cultures being very much larger and coarser than those in earlier cultures. In figure 5 are shown first transfers from cultures of blood taken, in each case, before serum was given and after completion of serum therapy. It is of interest that even in as many as three successive transfers from original cultures the difference in morphology previously described was retained in striking manner. What this definite change in morphology, possibly brought

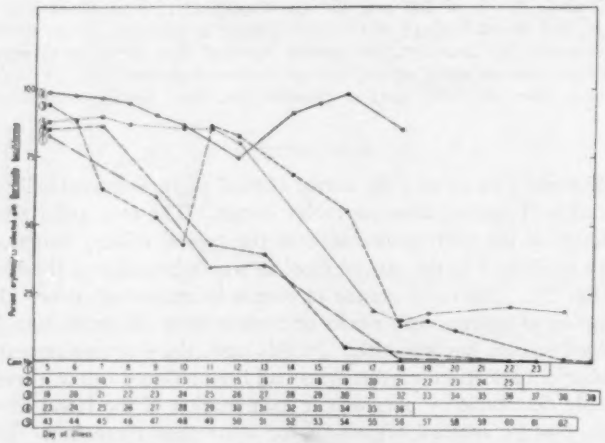

Fig. 4.—Infection of erythrocytes during the course of untreated Oroya fever (5 cases from Colombia).

about by passive immunization, signifies is not clear. One can only speculate on the possibility that it may represent a change in antigenic character, such as a transformation of a smooth to a rough type of growth or from a motile to a nonmotile state.

At any rate, there are indications, as seen in the reduction of visible infection of erythrocytes and in changes in number and morphology of colonies in the blood cultures, that specific immune serum does have some effect toward clearing the blood stream of organisms. A stronger serum might prove to be more completely effective in this regard.

The other laboratory data taken during the acute phase, in which the serum was given in each instance, showed no striking changes other than those associated with the gradual and slow general improvement which took place. The severe anemia showed little if any improvement in the absence of the usual supportive therapy, which was here entirely unobtainable. The titer of agglutinins had at first

been low in each case, as is usual in severe Oroya fever in its early stages. The sudden rise in titer of agglutinins is, of course, explainable by the administration of immune rabbit serum.

In the first case only were there significant changes in blood chemistry, namely a reversal of the serum albumin-globulin ratio and a strong indirect van den Bergh reaction. Damage to the liver was further suggested in this patient by the presence of jaundice more intense than that usually seen in Oroya fever, urobilin in the urine

Fig. 5.—First transfers from blood cultures before (tube on left) and after (tube on right) serum therapy. Small white colonies are seen suspended in semisolid agar medium. Top tubes, case 1; middle tubes, case 2; bottom tubes, case 3.

and a definitely enlarged liver. There may have been other factors at work here, besides the direct effect of a relatively severe degree of rapid hemolysis, although the patient had denied having had jaundice previously and having used alcohol extensively. Extensive hepatic damage, on the other hand, is known to occur frequently in severe Oroya fever,[4] and this adds the effects of an obstructive mechanism to the hemolytic jaundice already present.

4. Battistini, T. S.: Personal communication to the author.

SUMMARY AND CONCLUSIONS

Immune serum of high agglutinin titer was produced in rabbits by the intravenous administration of large amounts of B. bacilliformis, both in the fresh and in the formaldehyde-treated state. The titer obtained in rabbits inoculated with treated organisms was as high as that in animals inoculated with the untreated organisms.

Three cases of severe Oroya fever are reported in detail.

There was no dramatic change in the clinical picture in any of these cases as a result of immune serum therapy, except for the prompt appearance of the typical eruption in case 1. In this case, the time at which the eruption appeared was earlier in the course of the disease than is usual in untreated Oroya fever. This occurrence is as yet unexplainable.

It is thought that in these cases intravenous administration of immune rabbit serum may have caused an appreciable diminution in the percentage of erythrocytes infected with B. bacilliformis, as determined by examination of blood films. A comparison is made of these cases with 5 cases of severe untreated Oroya fever from Colombia. The reduction of visible erythrocyte infection appears to be much more gradual in these cases than in those in which immune serum was used in treatment.

Administration of immune serum in the 3 cases herein reported caused a diminution in the number of colonies of organisms obtained in serial blood cultures taken during the period of treatment. The type of colonies obtained in cultures taken before and after administration of serum indicated a change from finely granular and diffuse growth to a coarse and sparsely scattered type of growth. These changes are retained in transfers from original blood cultures, and their significance is not clear.

Dr. Telémaco S. Battistini, Director of the National Institute of Hygiene and Public Health, in Lima, Peru, provided laboratory space for the portion of this investigation carried out in Peru. Drs. E. E. Tyzzer, A. W. Sellards and Q. M. Geiman, of the Department of Comparative Pathology and Tropical Medicine of the Harvard Medical School, made available extensive facilities for the preparation of materials used in the course of this work. Drs. Carlos Protzel and José Jiménez Franco, of the Hospital Dós de Mayo, Dr. Guillermo Ricketts Rey de Castro, of the military hospital of San Bartolomé, and Dr. Victor Palti gave permission for the detailed study of the 3 cases herein reported. Dr. Hernando Groot, of Bogotá, supplied the data on the 5 cases of Oroya fever from Colombia.

RELATION BETWEEN HEPATIC AND PLASMA CONCENTRATIONS OF VITAMIN A IN HUMAN BEINGS

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To recognize clinical and subclinical vitamin A deficiency the blood level of vitamin A,[1] visual tests for night blindness,[2] biomicroscopic changes in the cornea [3] and other means have been used. The results obtained and the conclusions drawn have varied. Some authors have concluded that vitamin A deficiency is common [4]; others have considered it to be rare.[5]

The liver is the main storage place for vitamin A. It contains about 95 per cent of the total amount of the vitamin in the body.[6] Therefore, it can serve as an index of the vitamin A status. Hence, it would seem that those tests for deficiency of the vitamin would be significant which parallel low or absent stores in the liver.

The present study deals with the significance of the vitamin A level of the blood. The vitamin A concentration of human blood plasma was compared with the vitamin A content of biopsy specimens of the liver in continuation of previously reported studies.[7] In addition, the histologic distribution of vitamin A in the specimens of

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1. (*a*) Schneider, E., and Widmann, E.: Klin. Wchnschr. **14**:670, 1935. (*b*) Clausen, S. W., and McCoord, A. B.: J. Pediat. **13**:635, 1938. (*c*) Steininger, G.; Roberts, L. J., and Brenner, S.: Vitamin A in the Blood of Normal Adults, J. A. M. A. **113**:2381 (Dec. 30) 1939. (*d*) Lindqvist, T.: Acta med. Scandinav. (supp.) **97**:1, 1938. (*e*) Kimble, M. S.: J. Lab. & Clin. Med. **24**:1055, 1939.

2. (*a*) Jeans, P. C.; Blanchard, E., and Zentmire, Z.: Dark Adaption and Vitamin A, J. A. M. A. **108**:451 (Feb. 6) 1937. (*b*) Hecht, S., and Mandelbaum, J.: Relation Between Vitamin A and Dark Adaption, ibid. **112**:1910 (May 13) 1939; Am. J. Physiol. **130**:651, 1940. (*c*) Feldmann, J. B.: Instrument for Determining Course of Dark Adaption and for Measuring Minimum Light Threshold, Arch. Ophth. **12**:81 (July) 1934. (*d*) Young, G., and Wald, G.: Am. J. Physiol. **131**:210, 1940. (*e*) Isaacs, B. L.; Jung, F. T., and Ivy, A. C.: Vitamin A Deficiency and Dark Adaption, J. A. M. A. **111**:777 (Aug. 27) 1938.

3. Kruse, H. D.: Milbank Mem. Fund Quart. **19**:207, 1941.

4. Corlette, M. B., and Youmans, J. B.: Am. J. M. Sc. **195**:54, 1938. Jeghers, H.: Degree and Prevalence of Vitamin A Deficiency in Adults, J. A. M. A. **109**:756 (Sept. 4) 1937. Stiebeling, H. K., and Phipard, E. F.: Diets of Families of Employed Wage Earners and Clerical Workers in Cities, Circular 507, United States Department of Agriculture, 1939.

5. Hunt, E. P.: Milbank Mem. Fund Quart. **19**:252, 1941. Hecht and Mandelbaum.[2b]

6. (*a*) Moore, T.: Biochem. J. **25**:275, 1931. (*b*) Baumann, C. A.; Riising, B. M., and Steenbock, H.: J. Biol. Chem. **107**:705, 1934.

7. Meyer, K. A.; Popper, H.; Steigmann, F.; Walters, W. H., and Zevin, S.: Proc. Soc. Exper. Biol. & Med. **49**:589, 1942.

liver was studied by fluorescence microscopy. As previously shown,[8] this distribution varies greatly in normal and more in pathologic conditions. Consequently, the distribution of vitamin A was compared with the plasma and liver levels in order to understand better their relationship. At the same time a comparison between the histologic and the chemical methods was made.

In the course of this investigation additional data concerning vitamin A metabolism were collected, such as (*a*) the influence of anesthesia; (*b*) the results of feeding huge doses of the vitamin, and (*c*) the concentration of carotene in the plasma and in the liver.

The vitamin A content of the livers of rats has been compared with the vitamin A content of the blood by several investigators. Some investigators assumed a close parallelism between the vitamin in the liver and that in the blood[9]; others have failed to find it,[10] the results apparently depending on the experimental condition of the rats. Some relation between the vitamin A content of the blood and that of the liver has been found by Lewis, Bodansky and Haig[11] in infants studied post mortem. Our own examinations[7] of adults revealed parallelism only in certain conditions. To similar conclusions came Stewart and Rourke.[12]

That the relation between blood and liver concentrations of vitamin A in human adults is not simple is brought out by extensive chemical[13] and histologic[8b] examinations, which failed to show absence of vitamin A in any adult human liver. This speaks against the common occurrence of subclinical vitamin A deficiency in human beings. These contrasting results can be explained only by disturbances in the release of vitamin A from the liver, a possibiilty already suspected by Nylund and With[14] in 1941.

MATERIAL AND METHODS

The principal study concerns 76 patients operated on for conditions in the upper part of the abdomen (disease of the gallbladder, carcinoma of the stomach, peptic ulcer or carcinoma of the biliary tract and pancreas). The hepatic function was investigated by several procedures described in another paper.[15]

Because of studies reported,[16] some of the patients received 75,000 U. S. P. units of vitamin A[17] orally several days before operation. In all of them the vitamin A of the plasma

8. (*a*) von Querner, F.: Klin. Wchnschr. **14**:1213, 1935. (*b*) Popper, H.: Histologic Distribution of Vitamin A in Human Organs Under Normal and Under Pathologic Conditions, Arch. Path. **31**:766 (June) 1941; J. Mt. Sinai Hosp. **7**:119, 1940; Proc. Soc. Exper. Biol. & Med. **43**:234, 1940. (*c*) Meyer, K. A.; Popper, H., and Ragins, A. B.: Histologic Distribution of Vitamin A in Biopsy Specimens of Liver, Arch. Surg. **43**:376 (Sept.) 1941.

9. Lewis, J. M.; Bodansky, O.; Falk, K. G., and McGuire, G.: Proc. Soc. Exper. Biol. & Med. **46**:248, 1941; J. Nutrition **23**:351, 1942. Horton, P. B.; Murrill, W. A., and Curtis, A. C.: J. Clin. Investigation **20**:387, 1941.

10. Brenner, S.; Brookes, M. C. H., and Roberts, L. J.: J. Nutrition **23**:459, 1942. McCoord, A. B., and Luce-Clausen, E. M.: ibid. **7**:557, 1934. Leong, P. C.: Biochem. J. **35**: 806, 1941. Josephs, H. W.: Bull. Johns Hopkins Hosp. **71**:253, 1942.

11. Lewis, J. M.; Bodansky, O., and Haig, C.: Level of Vitamin A in the Blood as an Index of Vitamin A Deficiency in Infants and Children, Am. J. Dis. Child. **62**:1129 (Dec.) 1941.

12. Stewart, J. D., and Rourke, G. M.: Surgery **11**:939, 1942.

13. Moore, T.: Biochem. J. **31**:155, 1937.

14. Nylund, C. E., and With, T. K.: Acta med. Scandinav. **106**:202, 1941.

15. Meyer, K. A.; Steigmann, F.; Popper, H., and Walters, H. W.: Influence of Hepatic Function on Metabolism of Vitamin A, Arch. Surg. **47**:26 (July) 1943.

16. Popper, H.; Steigmann, F., and Zevin, S. S.: J. Clin. Investigation, to be published.

17. The product used was a vitamin A ester concentrate containing 200,000 U. S. P. units of the vitamin per gram, furnished by Distillation Products, Inc. of Rochester, N. Y. This was diluted with corn oil to contain 37,500 U. S. P. units per cubic centimeter.

had returned to a constant level before operation. To vary the nutritional status of the patients, 7 received three to seven daily doses of 500,000 U. S. P. units of the vitamin, which was discontinued several days before the operation. The vitamin in the blood had returned to a constant level before operation. In 51 patients the plasma content of vitamin A was determined before, during (immediately after the specimen of liver was taken for biopsy) and one hour after the operation.

To illustrate the ranges of the preliminary (before any vitamin A was given) vitamin A levels in our material, the plasma levels of the 167 subjects studied are shown in table 1.

The vitamin A level of the plasma was determined by the Carr-Price reaction. The extractions were made according to the method of Kimble[16] from 4 cc. of plasma (in only a few cases from 2 cc.). The purified benzine (petroleum ether) extracts were colorimetrically estimated for the concentration of carotene by potassium dichromate standards or by the photoelectric colorimeter. The calibration in both instances was done with pure crystalline beta carotene[18] in purified benzine. The readings for vitamin A were made in the majority of the cases with copper sulfate solutions according to a modification of Josephs' method[19]; in some cases the photoelectric colorimeter of Sheard and Sanford was used. The two methods checked satisfactorily (for 100 samples both methods were used, with maximal differences of 6 micrograms in levels below 100 micrograms per hundred cubic centimeters and 24

TABLE 1.—*Vitamin A and Carotene Levels of the Plasma in the Material Studied (Preliminary to Any Vitamin A Administration or Operation) Grouped According to Disease and Sex*

	Plasma Vitamin A Level in Micrograms per 100 Cc.								Average Plasma Carotene Level in Micrograms per 100	
	Males				Females					
Diagnosis	No. of Cases	Maximum	Minimum	Average	No. of Cases	Maximum	Minimum	Average	Males	Females
Hernia and fracture	10	48	19	32	..	..	..	..	64	..
Peptic ulcer	27	111	3	34	1	..	..	43	49	112
Miscellaneous diseases	16	55	2	30	..	..	..	..	51	..
Gallbladder disease without jaundice	3	38	20	27	24	66	17	34	68	49
Postinfectious condition	5	37	6	20	..	..	..	..	35	..
Carcinoma of gastrointestinal tract	16	44	0	18.5	2	..	..	19.5	61	17
Obstructive jaundice	14	16	0	4.0	4	17	0	7	94	51
Acute hepatitis	9	11	0	4	..	..	..	..	57	..
Cirrhosis of the liver	18	25	0	9	6	22	0	8	50	98
Vitamin A deficiency and sprue	..	..	..	..	2	0	0	0	..	9
Diseases of the kidney	8	210	14	84	..	..	..	..	79	..

micrograms in levels from 100 to 500 cc.). For the reading with copper sulfate standards the following steps were taken: The residue of the extract after evaporation of the purified benzine was taken up in 1 cc. of chloroform; 0.1 and 0.2 cc. of the chloroform solution were each transferred with a micropipet to test tubes of the same size as the standards. One-tenth cubic centimeter of chloroform was added to the test tube containing 0.1 cc. of chloroform extract, and then to each tube 1 cc. of a saturated solution of antimony chloride was added and a comparison was made immediately with the copper sulfate standards, the maximum color, which fades in a few seconds, being utilized. If the color with 0.1 or 0.2 cc. was too weak, a greater aliquot of the original chloroform solution was reduced by evaporation to 0.2 cc. for the reading. In each determination, readings of at least two concentrations were made, which had to check. For the photoelectric colorimeter 0.3 cc. of the chloroform extract was transferred to microcells and 1.8 cc. of antimony trichloride was added immediately before reading.

The copper sulfate standards and the photoelectric colorimeter were calibrated with chloroform solutions of two batches of crystalline vitamin A alcohol.[20] Since crystalline vitamin A is not stable in chloroform solution, probably because of ultraviolet irradiation,[21] care was taken to calibrate within twenty minutes after the crystals were dissolved in chloroform. During this interval, no appreciable loss of vitamin A was found by the Carr-Price reaction.

18. Received from the S. M. A. Corporation, Chagrin Falls, Ohio.
19. Josephs, H. W.: Bull. Johns Hopkins Hosp. **65**:112, 1939.
20. Supplied by Distillation Products, Inc., Rochester, N. Y.
21. Embree, N. D.: Indust. & Engin. Chem. **13**:144, 1941.

A second calibration was done with crystalline vitamin A in chloroform solution to which were added liver oils obtained from young rats kept on a vitamin A–deficient diet for twenty-seven days after weaning. The extracts were made by treating the livers as for vitamin A assay, to be described later. No appreciable difference was encountered in the calibration curves (fig. 1). The results are reported in micrograms per hundred cubic centimeters of plasma. The conversion factor of microgram to units is 3.28,[22] as we also found in determining three batches of vitamin A concentrates containing 200,000 U. S. P. units per gram.[20] For 36 patients duplicate determinations checked satisfactorily. For some of them, these duplicates were made only with 2 cc. of plasma.

After removal of grossly apparent capsule or vessels from the liver, biopsy specimens consisting of 0.1 to 0.4 Gm. of liver were saponified in double the amount of a 20 per cent aqueous solution of potassium hydroxide for forty-five minutes in a boiling water bath according to the method of Skurnik and Suhonen.[23] The hydrolysate was treated like the plasma, as previously described after addition of an equal volume of water. Occasionally the chloroform solution was diluted several times before the reading, to bring it into the range of the copper sulfate standards or the calibration curve. The hepatic concentration is recorded as micrograms per gram of fresh liver.

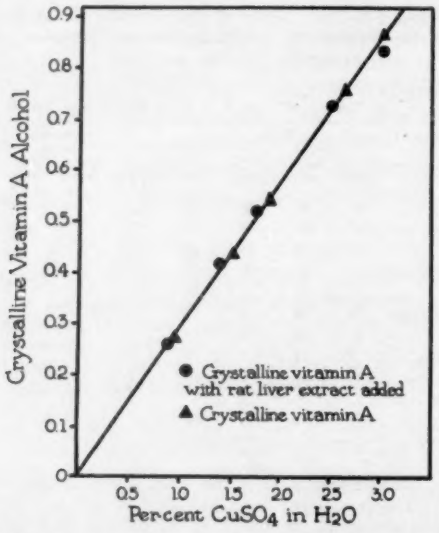

Fig. 1.—Calibration curve of copper sulfate solutions by chloroform solution of crystalline vitamin A with and without added liver oils obtained from vitamin A–deficient rats.

The saponification of blood is a moot question, since during saponification substances other than vitamin A may be liberated or destroyed, which might increase, reduce or interfere with the development of the Carr-Price reaction. In our experience in 45 cases, saponification of the plasma made no difference in values above 30 micrograms but may be significant below that level.

For neither the liver nor the plasma concentration of vitamin A was a correction made for the antimony trichloride color derived from the presence of carotene or carotenoids. The blue reaction due to vitamin A develops immediately and fades much faster than that due to carotene. Reliable information is not available as to how much of the immediate blue color is due to carotene. Our figures may, therefore, be influenced to a small degree by carotene.

22. Baxter, J. C., and Robeson, G. D.: J. Am. Chem. Soc. **64**:2411, 1942.
23. Skurnik, I., and Suhonen, P.: Ztschr. f. Vitaminforsch. **8**:316, 1939.

For histologic examination, the specimen of liver was fixed in solution of formaldehyde U. S. P. diluted 1:10. After one hour frozen sections were examined under the fluorescence microscope for content and distribution of vitamin A.[8b] Vitamin A gives a characteristic green fluorescence, which fades quickly owing to the irradiation. The specificity of this fluorescence has been established.[24] The exact localization of the fluorescence was examined in sections stained with methylene blue, which were studied both under ultraviolet rays and under visible light. The fat distribution was studied with an extremely sensitive fluorescent stain for fat, phosphin 3 R.[8b] Fluorescence photomicrographs were taken of each specimen for permanent record.[25] In addition, frozen sections were stained with sudan III. The rest of the fixed specimen was embedded in paraffin and submitted to routine histologic examination.

FINDINGS AND ANALYSIS

I. Vitamin A Levels in Our Material.—Table 1 shows the plasma vitamin A levels determined before vitamin A was administered and before any operation. Because of the particular population of a charity hospital, these levels may not compare with those found in healthy persons or in patients of an economically better class. In addition, the hospital diet may cause variations. The values are presented to show the preliminary levels of the material on which further studies have been made. Owing to technical reasons the majority of our 167 subjects were male, and statistical conclusions are thus possible only for them. In patients with peptic ulcer or disease of the gallbladder without jaundice, in patients with miscellaneous diseases and in those admitted because of hernia or fractures, an average level of between 27 and 34 micrograms was found. In renal disease, in agreement with prior reports,[26] the average level was much higher. Confirming the observations of Abels and associates,[27] our results showed that patients with a malignant gastrointestinal neoplasm had a plasma vitamin A level about half as high as the level of the aforementioned groups. In patients recovering from an infectious disease [28] and especially in those with hepatic disease or obstructive jaundice, low, and often zero, levels were encountered, which is in agreement with the clinical vitamin A deficiency found occasionally in these conditions.

Conclusion: The variation encountered in the preliminary levels of vitamin A in the plasma of the 167 patients studied agrees with observations made by others. In this material the average plasma level lies around 30 micrograms per hundred cubic centimeters.

II. Change of Vitamin A Level During Operation (Possibly Due to Anesthesia).—If the comparison between the vitamin A content of the plasma and of the liver is to be significant, the stability of the plasma vitamin A level must be examined during operation and anesthesia. Clausen and associates [29] have shown that after intake of alcohol the blood level of vitamin A rises owing to mobilization of vitamin A from the liver depots. On the other hand, the reduction of the prothrombin level (vitamin K) during anesthesia has been demonstrated.[30] Therefore, the

24. Popper, H., and Greenberg, R.: Visualization of Vitamin A in Rat Organs by Fluorescence Microscopy, Arch. Path. **32**:11 (July) 1941.

25. Popper, H., and Elsasser, M.: Canad. J. M. Technol. **3**:45, 1941.

26. (*a*) Hedberg, J., and Lindquist, T.: Acta med. Scandinav. **90**:331, 1939. (*b*) Clausen, S. W.; Baum, W. S.; McCoord, A. B.; Rydeen, J. O., and Breese, B. B.: J. Nutrition **24**:1, 1942.

27. Abels, J. C.; Gorham, A. T.; Pack, G. T., and Rhoads, C. P.: J. Clin. Investigation **20**:749, 1941.

28. Clausen, S. W., and McCoord, A. B.: J. Pediat. **13**:635, 1938. Thiele, W. S., and Scherff, J.: Klin. Wchnschr. **18**:1275, 1939.

29. Clausen, S. W.; Breese, B. B.; Baum, W. S.; McCoord, A. B., and Rydeen, J. O.: Science **93**:21, 1941. Clausen and others.[26b]

30. Allen, G. D., and Livingstone, H.: Anesthesiology **1**:89, 1940.

influence of anesthesia and operation on the plasma vitamin A level was studied. Of 51 subjects, 35 had identical plasma levels before, during and after operation (fig. 2 *B*). In 16, a minor decrease of the level was noted (fig. 2 *A*), which, analogous to some observations on vitamin K, might be due to the anesthesia.

The following types of anesthesia were used: spinal (29 subjects), ether induced (13 subjects) and cyclopropane induced (9 subjects). However, no significant difference between the various types of anesthesia were noted. According to these observations, a fairly constant plasma level may be assumed, which confirms the observations of Stewart and Rourke.[12] In all comparisons with the liver content to be described later, the vitamin A level of the plasma during operation was used.

Conclusion: The vitamin A level of the plasma does not appreciably change during operation.

III. Variation of the Vitamin A Content of the Liver.—The literature contains contradictory reports as to the variation of the content of vitamin A in different parts of the liver.[31] For 22 subjects we determined the vitamin A content from two different parts of the same biopsy specimen but found no significant difference.

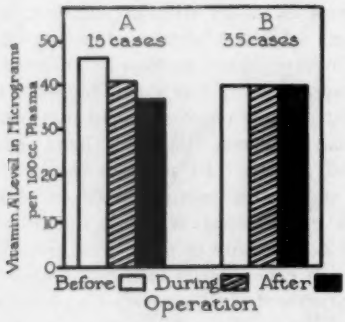

Fig. 2.—Averages of plasma vitamin A levels of 51 subjects before, during and after laparotomy. In 16 a slight decrease was found (*A*); in 35 no change was seen (*B*).

The maximum difference was 13 micrograms and the minimum 1 microgram, with an average difference of 4 micrograms. This confirms our own experiences with animal livers.

Since surgical procedures during laparotomy might influence the vitamin A concentration of the liver,[32] two separate biopsies were made on 2 subjects, at the start and at the end of the operation. No appreciable difference was encountered (first biopsy 61 and 70 micrograms and second biopsy 58 and 66 micrograms per gram, respectively), in confirmation of the studies of Stewart and Rourke.[12] Under the fluorescence microscope, the first and second biopsy specimens checked also.

Conclusion: No appreciable difference in the hepatic vitamin A concentration was found, in regard either to different parts or to the time of the biopsy.

IV. Comparison Between the Vitamin A Concentrations in the Plasma and in the Liver.—In our material the plasma vitamin A levels varied widely (fig. 3). Low levels were encountered chiefly in patients with jaundice; high levels were

31. Sen, K., and Sharma: Indian J. Vet. Sc. **6**:128, 1936. Rourke, G. M., and Stewart, J. D.: Composition of Liver, Arch. Path. **33**:603 (May) 1942. Lindqvist.[1d]
32. Young, G., and Wald, G.: Am. J. Physiol. **131**:214, 1940.

found mostly in patients who received large doses of vitamin A. Both these facts enabled us to compare the liver content with a wide range of the vitamin A level in the plasma. If in a greater number of cases the average hepatic content is compared with the average plasma level, a parallelism between the vitamin A concentration in the liver and that in the plasma may be construed and is apparent in the statistical consideration of section V. If, however, the cases are considered individually, no direct parallelism existed between the vitamin A concentration in the liver and that in the plasma. Thus, a liver content of 110 micrograms per gram was at times found with a plasma level of only 7 micrograms and in another instance with one of nearly 70 micrograms per hundred cubic centimeters. At

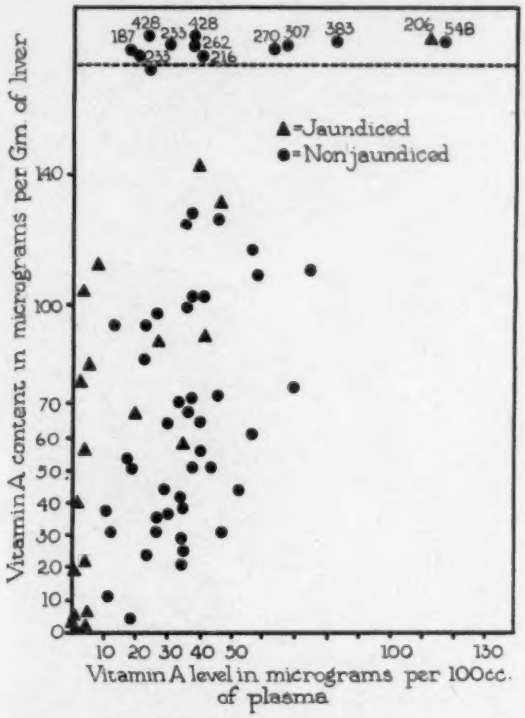

Fig. 3.—Vitamin A levels of the plasma during operation compared with the vitamin A content of biopsy specimens from the livers of patients with and patients without jaundice.

other times a liver content of 56 micrograms per gram was encountered in a patient with a plasma level of 50 micrograms per hundred cubic centimeters. However, in all subjects with high plasma vitamin A level (over 60 micrograms per hundred cubic centimeters) the hepatic concentration was high. Low or zero values for plasma vitamin A were encountered with both relatively high and relatively low vitamin A content in the liver. The discrepancy between the concentration in the plasma and that in the liver was especially great in patients with jaundice. In these the plasma level was usually low despite a normal or only slightly decreased hepatic concentration of vitamin A.

Conclusion: The vitamin A content in the plasma and that in the liver display a parallelism only when the plasma level is high.

V. Comparison Between the Vitamin A Content of the Plasma and of the Liver and the Histologic Distribution of Vitamin A.—Comparison of Vitamin A Fluorescence and Vitamin A Content of the Liver: In animal experiments under varied conditions, a parallelism between the vitamin A content (chemical) and the amount of vitamin A fluorescence was proved,[33] whereas in human subjects this parallelism seems questionable.[34] This study enabled us to compare the histologic and chemical methods as applied to the human liver.

In table 2 the total amount of vitamin A fluorescence is indicated by symbols and compared with the chemical assay. With few exceptions, the results of the two

TABLE 2.—*Comparison Between the Results of the Chemical Assay for Vitamin A and the Total Amount of Vitamin A Fluorescence in Biopsy Specimens of Human Liver, Arranged in Order of Chemical Vitamin A Content*

Vitamin A Content, Micrograms/Gm. of Liver	Estimated Total Amount Vitamin A Fluorescence	Vitamin A Content, Micrograms/Gm. of Liver	Estimated Total Amount Vitamin A Fluorescence	Vitamin A Content, Micrograms/Gm. of Liver	Estimated Total Amount Vitamin A Fluorescence	Vitamin A Content, Micrograms/Gm. of Liver	Estimated Total Amount Vitamin A Fluorescence
0.2	± to −	37	+ to ++	70	+	121	+++
3.3	± to −	37	++	71	+ to ++	123	+++
3.5	±	41	+	71	++	124	+++
5	±	41	+ to ++	74	+	127	++ to +++
5.6	±	41	++	74	++	138	++
7	±	47	+	80	+	140	+++
10	±	49	++	80	++	167	+++
11	±	49	+++	86	++	187	++ to +++
19	++	50	+	88	+ to ++	206	+++
20	+	52	+ to ++	91	++	216	+++ to ++++
22	+	55	+	92	+	232	+++
24	+	55	++	96	++	232	++ to +++
25	++	56	++	97	++ to +++	262	+++
29	+	59	++	99	++ to +++	269	++++
30	++	60	++	100	+++	307	+++
31	++	62	+ to ++	106	+++	402	++++
31	++	63	+ to ++	108	++	428	+++
35	+ to ++	68	+ to ++	110	++	428	++++
37	+	68	++	113	+++	548	++++
37	+						

methods check. With some practice one is able from the histologic picture to predict the chemical result closely.

Owing to this parallelism, the relation between the plasma vitamin A level and the total vitamin A fluorescence in the liver was found the same as between the plasma vitamin A level and the chemical assay.

Irregularity of Distribution of Vitamin A Fluorescence: In normal human liver (fig. 4 *A* and *B*) vitamin A fluorescence is imparted by lipids in Kupffer cells and in the epithelial cells by fine lipid droplets at the edge of the cells, by a few medium-sized or large fat droplets, by lipofuscin, by mitochondria and by the cytoplasm. Some of the these lipids may not be demonstrable by sudan III but

33. Popper, H., and Brenner, S.: J. Nutrition **23**:431, 1942.

34. Schairer, E.; Rechenberger, J.; Gockel, H., and Patzelt, K.: Virchows Arch. f. path. Anat. **305**:360, 1939.

are visualized by staining with phosphin 3 R. The vitamin A distribution varies somewhat, even with identical total amounts of vitamin A and in livers which are normal on routine histologic examination [8b] (fig. 4 *C*).

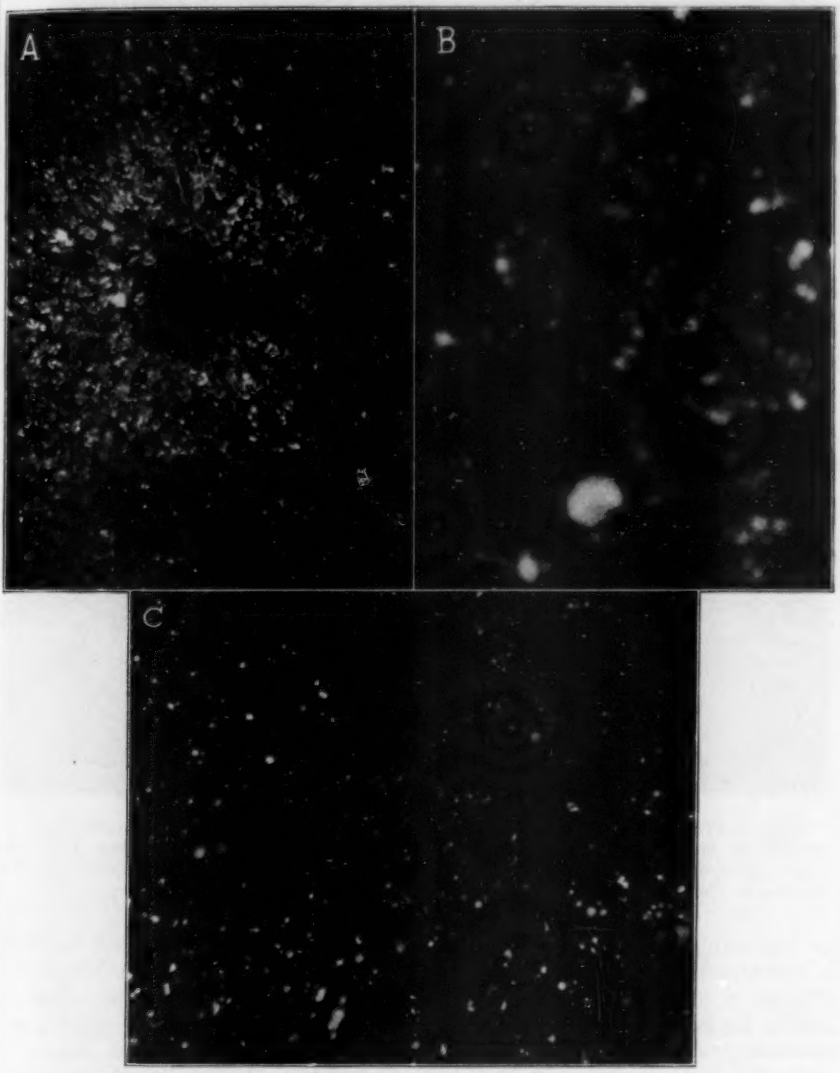

Fig. 4.—Fluorescence photomicrographs of biopsy specimens of liver: *A*, normal distribution of the vitamin A fluorescence which is imparted by Kupffer cells, fine lipid droplets in liver cells and by a few irregularly scattered, large fat droplets; the diffuse dull fluorescence of the cytoplasm is not recognized in this photograph; *B*, high power field of a human liver with regular vitamin A fluorescence imparted by relatively large droplets in the Kupffer cells and by fine droplets at the edge of the liver cells; *C*, slightly irregular distribution of the vitamin A fluorescence in a liver without any signs of parenchymatous damage on routine histologic examination.

Actually, no human liver examined showed the even and regular distribution of the vitamin A fluorescence found in experimental animals, which suggests that in patients coming to operation the structure of the liver is not completely normal. Practically all human livers examined by routine histologic methods showed some changes in the periportal fields, i. e. round cell infiltration. Pathologic changes of the parenchyma, however, are less easily recognized by routine examination. The deviations of the fluorescence microscopic picture from the normal are: prevalence of vitamin A in Kupffer (fig. 5 *A*) or liver cells (fig. 5 *B*); development of medium-sized to large-sized fat droplets with high, low, absent or varying vitamin A fluorescence (fig. 6 *A*, *B* and *C*); irregular distribution throughout the cytoplasm of the liver cells of small to medium-sized fluorescent fat droplets which normally are distributed only at the edge of the cells; bizarre shapes of the Kupffer cells outlined by the fluorescent lipid droplets in them (fig. 7 *A*); great variation

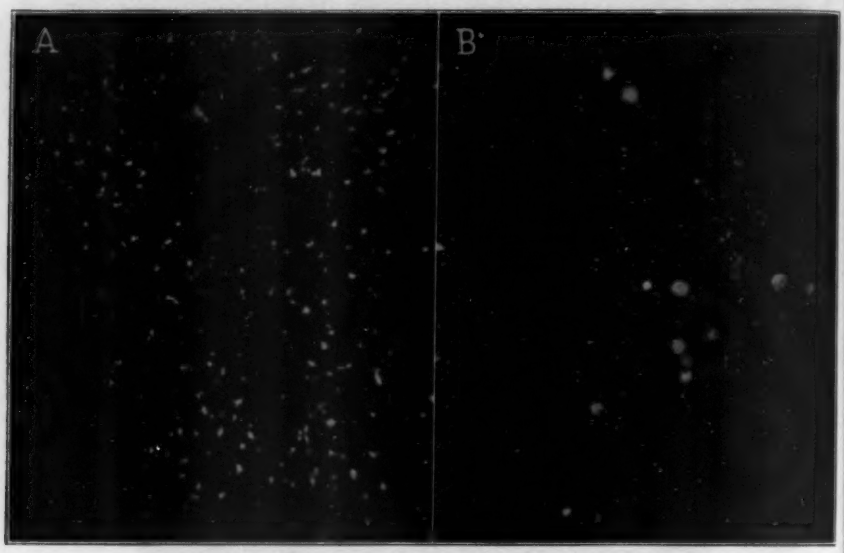

Fig. 5.—Fluorescence photomicrographs of biopsy specimens of liver: *A*, marked vitamin A fluorescence imparted almost exclusively by the Kupffer cells; *B*, marked vitamin A fluorescence almost exclusively imparted by fine droplets and a few irregularly scattered, large fat droplets in the liver cells.

in the morphologic details from cell to cell, often characterized by small foci with a fluorescent vitamin A pattern completely different from the other (fig. 7 *B*). Not all of these variations are apparent in visible light. Some of the variations within the lobules are limited to certain areas of the lobule and are probably not pathologic but rather due to functional changes. Such variations are also found in healthy experimental animals under varied nutritional conditions.[35] Thus, the absence of vitamin fluorescence from the immediate central or peripheral areas is not necessarily pathologic. The diffuse vitamin A fluorescence of the cytoplasm varies greatly. If to these variations of the vitamin A fluorescence the appearance of other fluorescent details are added, such as brown-red lipofuscin fluorescence.

35. Popper, H., and Steigmann, F.: To be published.

green, not fading, bilirubin fluorescence, black spots due to lack of fluorescence of the bile casts and red hematoporphyrin fluorescence as seen in some cirrhoses, an impressive variability of the fluorescence picture may result. In table 3 the degree of variability is compared with the incidence of pathologic changes on routine histologic examination associated with the average liver and plasma levels of vitamin A. In the subjects with marked variability, pathologic changes of the

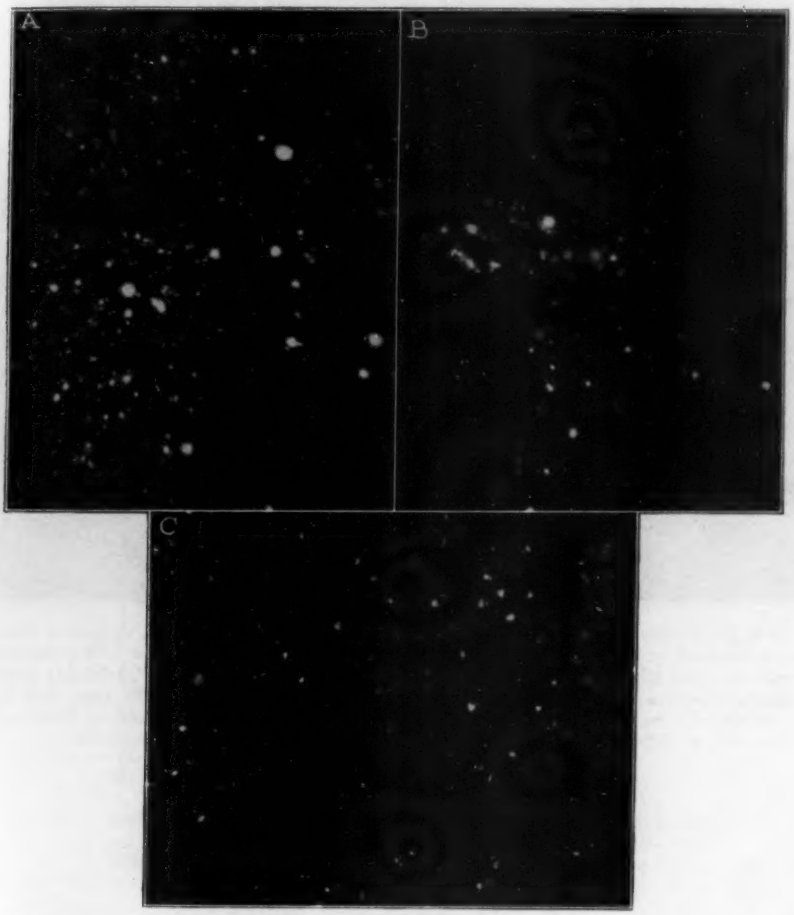

Fig. 6.—Fluorescence photomicrographs of biopsy specimens of liver: *A*, marked vitamin A fluorescence of large, fat droplets, which is stronger than that of the Kupffer cells, in a liver which appears normal on routine histologic examination; *B*, variable vitamin A fluorescence in the large fat droplets in a cirrhotic liver (a few bizarre-shaped Kupffer cells impart vitamin A fluorescence); *C*, fat droplets showing nearly no vitamin A fluorescence as compared with the marked fluorescence of the Kupffer cells in a patient with disease of the gallbladder without jaundice.

parenchyma, such as central and miliary necroses and interstitial hepatitis, are encountered; the plasma and liver concentration of vitamin A shows a tendency to be low. The latter corresponds to the low vitamin A fluorescence usually

TABLE 3.—*Relation Between Degree of Disturbance of Vitamin A Fluorescence Pattern and Pathologic Changes in the Liver and the Vitamin A Concentration in Liver and Plasma*

Degree of Disturbance of Vitamin A Fluorescence Pattern	Number of Subjects	Pathologic Changes in Liver		Average Concentration of Vitamin A	
		Number of Subjects	Percentage	Mg./Gm. of Liver	Mg./100 Cc. of Plasma
Plus-minus	6	0	0	130	38
Plus	26	2	8	143	38
2 plus	24	3	12	104	31
3 plus	13	10	77	51	14.5
4 plus	7	7	100	27	7

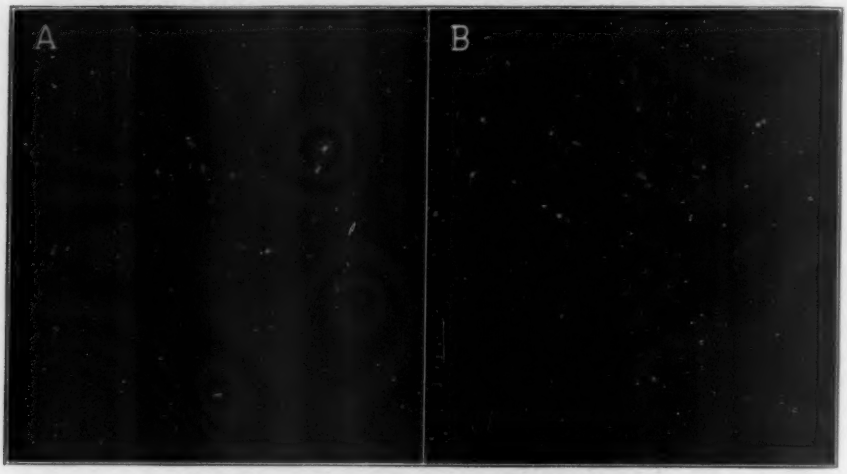

Fig. 7.—Fluorescence photomicrographs of biopsy specimens of liver: *A*, vitamin A fluorescence imparted by a few bizarre-shaped Kupffer cells in a jaundiced patient with a malignant neoplasm of the biliary tract and low hepatic concentration of vitamin A; *B*, relatively marked vitamin A fluorescence imparted by Kupffer cells and fine droplets in the liver cells in a circumscribed area, whereas the surrounding areas are almost devoid of vitamin A fluorescence (there was no difference between the two areas on routine histologic examination).

TABLE 4.—*Relation Between the Vitamin A Fluorescence in the Kupffer Cells and Liver Cells as Compared with the Pathologic Changes in the Liver and with the Vitamin A Concentration in Liver and Plasma*

	Degree of Prevalence of Vitamin A Fluorescence in Kupffer Cells Over That in Liver Cells			Vitamin A Fluorescence Equal in Kupffer Cells and Liver Cells	Degree of Prevalence of Vitamin A Fluorescence in Liver Cells Over That in Kupffer Cells		
	3 Plus	2 Plus	1 Plus		1 Plus	2 Plus	3 Plus
Number of subjects	5	13	21	23	8	5	1
Percentage with pathologic changes	20	15	19	44	50	20	0
Average vitamin A concentration in micrograms per gram of liver	177	147	133	69	51	43	41
Average vitamin A concentration in micrograms per 100 cc. of plasma	53	35	35	25	20	20	27

observed in association with great variability of the histologic picture. At present the cause and significance of most of the variations is unknown. It may be suspected that the absence of vitamin A from the fat often encountered in cirrhosis may have something to do with choline deficiency.[36] Some variation may be caused by other nutritional alterations.

Prevalence of Vitamin A Fluorescence in Kupffer Cells: The prevalence of vitamin A in Kupffer cells has been noted when the vitamin is fed in excess.[37] Generally when high amounts of vitamin A are found, the Kupffer cells are rich in

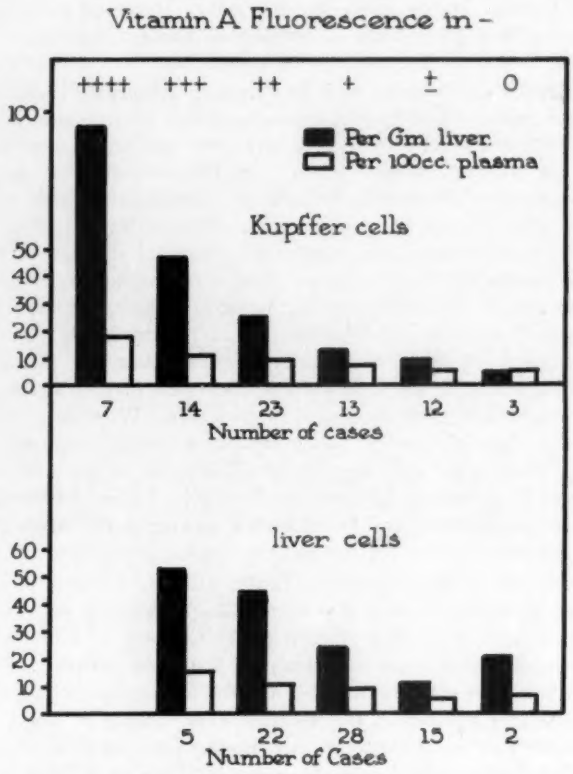

Fig. 8.—Comparison of the degree of the vitamin A fluorescence in Kupffer cells and in liver cells with the concentration of vitamin A in liver and plasma.

it.[8b, c] This study provides an opportunity to compare the amount of vitamin A fluorescence in Kupffer cells and in liver cells with the concentrations in the plasma and the liver (fig. 8). If average levels are compared, the amount of vitamin A fluorescence in Kupffer cells is in proportion to the total amount of vitamin A in the liver. The vitamin A fluoresence in the liver cells varies also proportionally but

36. Popper, H., and Chinn, H.: Proc. Soc. Exper. Biol. & Med. **49**:202, 1942.

37. Hirt, A., and Wimmer, K.: Klin. Wchnschr. **19**:123, 1940. Popper and Greenberg.[24] Popper and Brenner.[33]

to a lesser degree, shown by the fact that an extremely high (4 plus) vitamin A fluorescence in the liver cells was never found. The variation of the plasma level in comparison with vitamin A fluorescence in the Kupffer and liver cells is not marked.

The points emphasized are borne out by table 4, in which the observations are analyzed as to prevalence of vitamin A fluorescence in either Kupffer or liver cells. The higher the liver level the greater is the prevalence of the vitamin A fluorescence of the Kupffer cells over that of the liver cells, whereas the plasma levels are not as closely related. One may assume that, as in animals, excessive amounts of vitamin A in the liver are stored in the Kupffer cells. However, as in the experimental animals, not enough evidence is present to connect the high vitamin A fluorescence of the Kupffer cells with the vitamin A level in the plasma.

Analysis of Results on Subjects with Discrepancy Between Plasma and Liver Vitamin A Concentration: The fluorescence microscopic examination may be used to explain the discrepancy between plasma and liver vitamin A and also to aid in interpreting low or zero plasma levels. In this investigation we observed 6 instances of discrepancy between the vitamin A concentrations in the plasma and liver (table 5). The tests of hepatic function, when performed, showed severe impairment. The routine histologic examination revealed damage of the parenchyma. In all instances the distribution of vitamin A was highly irregular; there was, however, no specific disturbance of the pattern. The cytoplasm of the liver cells showed much green bilirubin fluorescence, and many black bile casts were seen. The fat droplets did not show vitamin A fluorescence, nor did most of the Kupffer cells. When Kupffer cells did show it, they were bizarre in shape and not adjacent to liver cells manifesting vitamin A fluorescence. When fine lipid droplets regularly lined the edges of the cells, they showed a rather irregular vitamin A fluorescence (fig. 9*A*). All this suggests a disturbance in the normal relation between storage in Kupffer cells and that in liver cells. This, however, was not restricted to these subjects only and hence cannot be considered solely responsible for the discrepancy between the plasma and the liver concentration of vitamin A.

Analysis of Results on Subjects with Plasma Vitamin A Level of Zero: All 7 patients showed great variation of the vitamin A fluorescence pattern. In 1 of them the Kupffer cells only showed vitamin A fluorescence; in 2 of them nothing was seen in the Kupffer cells, while the remaining 4 showed vitamin A fluorescence in irregular distribution in both the Kupffer and the liver cells. The few scattered Kupffer cells imparting vitamin A fluorescence were bizarre in shape. In liver cells the fluorescence was found chiefly in medium-sized and large-sized fat droplets in an irregular distribution. In 3 subjects, many fat droplets without fluorescence were encountered; even fine lipid droplets at the edge of the cells failed to show vitamin A fluorescence. The characteristic feature in this group was irregular distribution and prevalence of fat without vitamin A fluorescence (fig. 9*B*).

Analysis of Results on Subjects with Plasma Vitamin A Level Below 7 Micrograms per Hundred Cubic Centimeters: Six patients with a plasma vitamin A level above zero but below 7 micrograms revealed great variation in the vitamin A distribution. Most of them showed vitamin A fluorescence only in the intermediate zone, while in the central area there were usually biliary deposits and often biliary necrosis. The peripheral area revealed large cells with dark cytoplasm without vitamin A or fat. In most much brown fluorescent pigment of the nature of lipofuscin or iron was seen. Usually more vitamin A fluorescence was observed

TABLE 5.—*Laboratory Data in Cases of Marked Discrepancy Between Plasma Vitamin A Level and Hepatic Vitamin A Concentration*

Subject	Diagnosis	Vitamin A Concentration		Degree Vitamin A Fluorescence			Findings on Clinical Tests of Liver Function								
		Micrograms/100 Cc. of Plasma	Micrograms/Gm. of Liver	Total	In Kupffer Cells	In Liver Cells	Observations on Routine Histologic Examination	Excretion of Hippuric Acid, Gm.	Excretion of Alimentary Galactose Gm.	Phosphatase, Units	Cephalin Flocculation Reaction	Albumin/Globulin	Total Cholesterol/Cholesterol Esters	Icterus Index	Takata-Ara Reaction	Nonprotein Nitrogen	Urinary Urobilinogen, Mg./24 Hr.
P.M.	Obstructive Jaundice with biliary cirrhosis	0	40	Not examined			Biliary cirrhosis with extensive recent necrotizing changes	3.6	...	..	—	4.6/3.8	200/131	150	++++	31	..
J.K.	Cholangitis	0	50	+	+	+	Cholangitis and cholangiolitic abscesses; toxic edema and Kupffer cell mobilization in the surrounding liver tissue	4.0	0.6	40	++	3.4/2.3	305/241	37	O	54	20
M.B.	Obstructive Jaundice from carcinoma of pancreas	7	110	++	+	++	Central biliary necrosis, Kupffer cell mobilization in intermediary and peripheral zone; fibrosis of periportal fields with bile duct proliferation	1.0	...	..	—	.....	394/196	..	—	34	4
J.N.	Benign obstruction of the common duct with Jaundice	4	80	++	±	++	Beginning Interstitial hepatitis with intensive leukocytic infiltration	1.9	...	..	—	.....	.....	43	—	30	..
E.D.	Obstructive Jaundice from carcinoma of pancreas	6	55	+	±	+	Miliary necrosis surrounded by leukocytic infiltration; extensive fibrosis and leukocytic infiltration of the periportal field	1.14	...	12	++	2.9/2.5	147/42	75	O	42	9.08
H.B.	Obstructive Jaundice with biliary cirrhosis	0	74	+	+	±	Irregular size of liver cells; extensive central biliary necrosis; fibrosis and leukocytic and lymphocytic infiltration of the enlarged periportal field with regeneration of the surrounding parenchyma	2.5	...	58	—	3.3/3.4	200/33	100	++	31	..

in the Kupffer cells than in the liver cells, the cytoplasm being free of vitamin A. The fine droplets occasionally observed at the edge of the cell were irregularly distributed and were usually not in the vicinity of Kupffer cells with vitamin A fluorescence.

Conclusion: Vitamin A fluorescence in the human liver parallels the hepatic concentration determined chemically. If high amounts of vitamin A are present in the liver, they are stored chiefly in the Kupffer cells. The normal pattern of distribution of the vitamin is altered if there is minor parenchymal damage; with severe damage the pattern presents greater changes than the alterations noted on routine histologic examination. These variations are marked in the case of

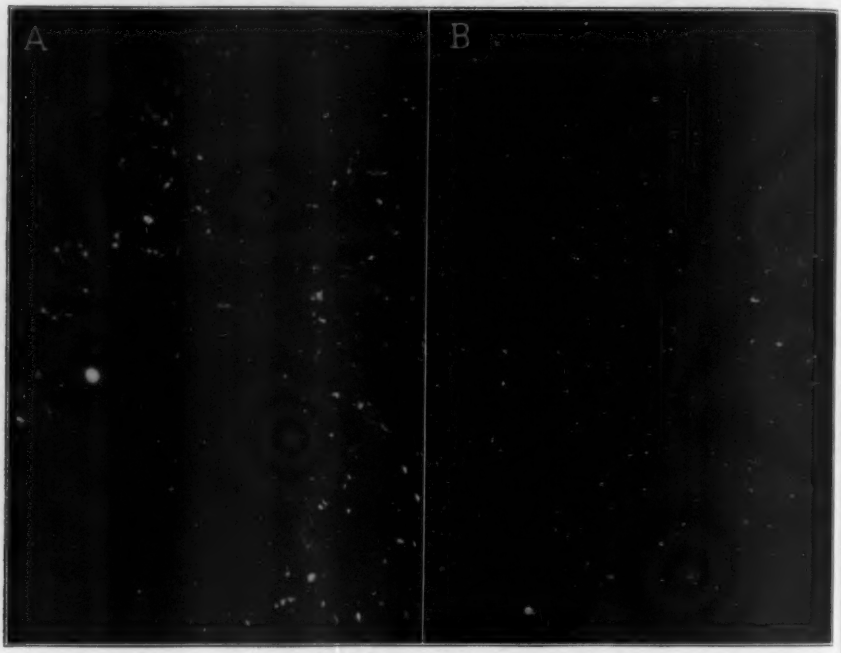

Fig. 9.—Fluorescence photomicrographs of biopsy specimens of liver: *A*, rather marked vitamin A fluorescence in extremely irregular distribution imparted by irregularly shaped Kupffer cells and by fat droplets of varying sizes and uneven distribution in the liver cells in a patient with obstructive jaundice and marked discrepancy between the hepatic concentration of vitamin A and the low plasma vitamin A level; *B*, slight vitamin A fluorescence imparted by a few Kupffer cells and isolated small fat droplets in liver cells in a patient with low vitamin A concentration in liver and plasma (malignant neoplasm of the biliary tract).

subjects with low blood levels of vitamin A, although pathognomonic morphologic changes could not be made out.

VI. Effect of Administration of Large Doses of Vitamin A.—In all 7 subjects who received the huge supplements, of 500,000 U. S. P. units of vitamin A daily, the plasma level rose strikingly. Even zero levels, as in jaundice, and low levels, as in pyloric obstruction, reached at least normal levels (table 6). The vitamin A content of the liver was extremely high, even in the presence of hepatic damage. Although no preliminary hepatic levels were available, the assump-

TABLE 6.—*Data on Patients Who Received Several Doses of 500,000 U. S. P. Units of Vitamin A Before Operation*

Name	Age	Sex	Diagnosis	Amount of Vitamin A Ingested, U.S.P. Units	Vitamin A Level, Micrograms/100 Cc. of Plasma		Amount of Vitamin A, Micrograms per Gm. of Liver	Carotene Level, Micrograms/100 Cc. of Plasma		Carotene Level, Microgram per Gm. of Liver	Vitamin A Fluorescence			Clinical Evidence of Hepatic Damage	Routine Histologic Evidence of Hepatic Damage
					Preliminary	At Operation		Preliminary	At Operation		Total	In Kupffer Cells	In Liver Cells		
J.S.	51	M	Carcinoma of stomach	2,650,000	10	44	123	59	56	13	+++	++++	O	O	Slight lymphocytic infiltration of periportal fields
L.O.	28	M	Carcinoma of stomach	1,650,000	17	35	428	44	35	11	++++	++++	++	+	Slight lymphocytic infiltration of periportal fields
G.B.	56	M	Carcinoma of stomach	3,075,000	44	109	548	147	147	2.7	++++	++++	+++	O	Fibrosis and lymphocytic infiltration of periportal fields
J.H.	33	M	Tuberculosis of the stomach with pyloric obstruction	3,575,000	2.3	63	307	7.3	Trace	1.7	+++	+++	++	+	Kupffer cell mobilization with circumscribed small necroses
M.B.	69	F	Cholelithiasis without jaundice	2,650,000	27	77	383	73	73	14	++++	++++	++	±	Irregular mitoses of liver cells; lymphocytic infiltration of periportal fields
J.D.	62	M	Cholelithiasis with jaundice	2,650,000	44	105	205	47	50	4.3	++++	++++	+	+	Interstitial hepatitis; diffuse leukocytic and lymphocytic infiltration of parenchyma and periportal fields
W.Mc.	60	M	Obstructive jaundice from carcinoma of ampulla of Vater	2,575,000	0	33	126	118	73	8	++	++	±	±	Central necroses; lymphocytic and leukocytic infiltration of enlarged periportal fields

tion can be made that rather high amounts of vitamin A have been deposited in the liver. No increase of the carotene deposit, however, can be assumed.

The average amount of vitamin A in the liver of 5 nonjaundiced subjects receiving 500,000 U. S. P. units of vitamin A daily was 366 micrograms per gram.

Fig. 10.—Fluorescence photomicrograph of a biopsy specimen of liver from a patient without hepatic damage after he had received six daily doses of 500,000 U. S. P. units of vitamin A (pronounced vitamin A fluorescence imparted chiefly by the Kupffer cells and only to a smaller extent by fine lipid droplets at the edge of the liver cells).

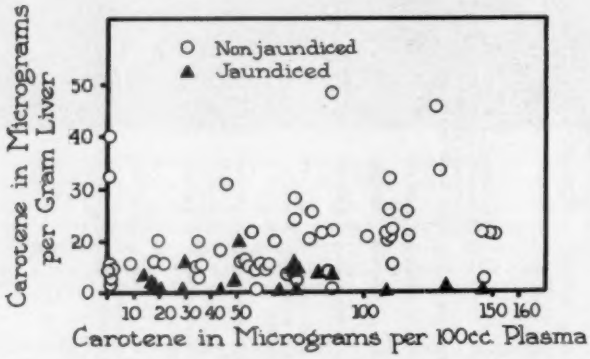

Fig. 11.—Carotene levels of the plasma during operation compared with the carotene content of biopsy specimens of liver from patients with and from patients without jaundice.

If 100 micrograms is taken as the average hepatic concentration, an increase of 266 micrograms can be assumed. In a liver of 1,500 Gm. the amount stored would be 390,000 micrograms or, with a conversion factor of 3.28, 1,279,200 U. S. P. units of vitamin A. The patients received an average of 3,150,000 U. S. P.

units each. Hence, one might presuppose that almost one half of the amount fed has been stored in the liver.

For 2 jaundiced subjects a similar comparison is impossible since an average of the hepatic concentrations of vitamin A could not be taken and the size of the liver was also unknown. If the latter is assumed to have weighed 1,500 Gm., it would mean that the average total amount was 811,800 U. S. P. units. Since they each received 2,600,000 units of vitamin A, definitely much less had been stored in their livers than in normal livers, even if it is assumed that no vitamin A was previously present in the liver.

Also histologically by fluorescence microscopy extremely high amounts of vitamin A were encountered in the livers of all these patients. The vitamin A fluorescence was predominantly seen in the Kupffer cells (fig. 10). In the 2 jaundiced subjects the vitamin A was seen not only in the pathologic areas, as in the fat droplets, but in the normal sites, in Kupffer and in liver cells.

Conclusion: After administration of huge amounts of vitamin A, the vitamin A content of the human liver is increased strikingly even in jaundiced subjects, although to a somewhat lesser degree than in nonjaundiced subjects. The plasma level of the vitamin rises, but not to the same extent.[13]

VII. Studies on Carotene.—For all subjects studied, the level of carotene in the plasma and in the liver has been determined simultaneously with that of the vitamin A. A review of the carotene level in the specimens of plasma examined failed to show similar relations to diseases as the vitamin A level (table 1). During operation and during anesthesia no changes of the carotene level of the plasma were noted. Figure 11 shows that no definite relationship could be elicited between the carotene concentrations in the plasma and in the liver. The only noteworthy observation was that in jaundiced patients the level of carotene in the liver is usually low, which confirms the observations of Ralli and co-workers.[38]

Conclusion: No characteristic behavior was indicated from the determinations of the carotene levels in plasma and in the liver.

COMMENT

The comparison between the vitamin A concentration in biopsy specimens of liver and the plasma shows that on the average subjects with a high hepatic concentration have a high plasma level and that subjects with a low plasma level have a low hepatic concentration. If, however, values for individual subjects are taken, no direct relation exists between the plasma level and the hepatic concentration of vitamin A. Similar results are found in the tables of Stewart and Rourke [12] and Abels and associates.[39] An attempt to use the plasma vitamin A level as an index of the vitamin A depots of the body of an individual subject is justified only if the plasma level is normal or, better still, if it is high, since a high plasma level points to a normal or high hepatic concentration. A low plasma level, on the other hand, does not necessarily indicate depleted liver stores. Since low plasma levels may coincide with normal or depleted liver depots, the question arises whether in subjects with normal liver depots and low plasma levels clinical vitamin A deficiency exists; in other words, whether the plasma level or the liver

38. Ralli, E. P.; Papper, E.; Paley, K., and Bauman, E.: Vitamin A and Carotene Content of Human Liver in Normal and in Diseased Subjects, Arch. Int. Med. **68**:102 (July) 1941.

39. Abels, J. C.; Gorham, A. T.; Pack, G. T., and Rhoads, A. B.: Proc. Soc. Exper. Biol. & Med. **48**:488, 1941.

content indicates the vitamin A status of the body and thus the requirements for supplements of the vitamin.

Primarily, one would be inclined to consider the liver level, which represents the vitamin A depots in the body, as an index of the vitamin A status. However, the results of fluorescence microscopic examination of the biopsy specimens of liver point rather to the plasma level as the indicator of the vitamin A status. The distribution of the vitamin A fluorescence varies greatly, which indicates that chemically identical amounts stored may have different functional significance. In animal experiments [40] we were able to show that in hepatic damage vitamin A shifts from normal sites, represented by Kupffer cells and by fine droplets at the edge of the liver cell, to pathologic sites, represented by large fat droplets. Furthermore, if carbon tetrachloride–intoxicated rats are kept on a vitamin A–deficient diet, the vitamin A in the pathologic sites is less available for utilization. The vitamin A remains longer in the fatty than in the normal areas. In human material a disturbance of the distribution also occurs. Some degree of it was found in every specimen. It is more marked in pathologic livers, although less uniformly than in the livers of the carbon tetrachloride–intoxicated animals. This disturbance of vitamin A distribution is especially pronounced in patients with jaundice. Thus, a shift of the vitamin A fluorescence from the Kupffer cells and fine droplets at the edge of the liver cells in human beings results in a very irregular and sometimes very bizarre picture, with a disturbance of the normal topographic relation between vitamin A fluorescence of Kupffer cells and liver cells.

All these changes indicate, in addition to the disturbance of the general hepatic function, severe disturbance of the vitamin A metabolism within the liver. Patients with discrepancy between plasma level (low) and liver stores (quantitatively normal) usually showed pathologic hepatic function on clinical examination and parenchymatous damage on routine histologic examination. All showed severe disturbances of the vitamin A distribution, although a specific morphologic picture associated with such a discrepancy could not be ascertained. The disturbance in the distribution may explain the impaired release of vitamin A from the liver. Disturbances in the release of vitamin A were already suggested by several facts: In young rats the first signs of vitamin A deficiency appear after exhaustion of the liver depots,[41] whereas in older rats [42] and in other animals [43] traces of vitamin A may be found in the liver at such a time. In human subjects, moreover, night blindness may appear while there is still considerable vitamin A in the liver. Thus, in diabetes mellitus [44] as well as in thyrotoxicosis [45] night blindness as a sign of vitamin A deficiency and even low blood levels [46] have been reported, in spite of the fact that the cadaver liver of a subject with this disease usually contains con-

40. Popper, H.; Steigmann, F., and Dyniewicz, H. A.: Proc. Soc. Exper. Biol. & Med. **50**:266, 1942.

41. Dann, W. J.: Biochem. J. **26**:1072, 1932. Baumann, Riising and Steenbock.[6b] Brenner, Brookes and Roberts.[10] Popper and Greenberg.[24]

42. Davies, A. W., and Moore, T.: Biochem. J. **31**:172, 1937.

43. Guilbert, H. R., and Hart, G. H.: J. Nutrition **8**:25, 1934. Guilbert, H. R., and Hinshaw, R.: ibid. **8**:45, 1934. Leong, P. C.: Biochem. J. **35**:806, 1941.

44. Brazer, J. G., and Curtis, A. C.: Vitamin A Deficiency in Diabetes Mellitus, Arch. Int. Med. **65**:90 (Jan.) 1940.

45. Wohl, M. G., and Feldman, J. B.: Endocrinology **24**:389, 1939. Zaffke, K. H.: Arch. f. Ophth. **140**:61, 1939.

46. Wendt, H.: München. med. Wchnschr. **82**:1660, 1935. Lindqvist.[1d]

siderable amounts of vitamin A.[47] Lindqvist [2c] found in pneumonia low serum levels of vitamin A but normal depots in the liver at necropsy.

Many metabolites show an equilibrium in their balance between blood and liver. In the case of some metabolites, e. g. dextrose,[48] the blood level regulates the liver storage. In the case of vitamin A, on the other hand, at least under normal conditions the plasma level is obviously regulated and maintained by the liver. The liver is able to maintain for a certain length of time a normal blood level, even without nutritional supply.[49] In pathologic conditions this regulation by the liver is impaired, as seen from the data for subjects with a high hepatic concentration and a low plasma level. This disturbance of the release makes the plasma level more important for the recognition of vitamin A deficiency than the hepatic concentration, because only the circulating vitamin A is of functional value. Acute hepatic damage presents an example of this. The low plasma vitamin A level [50] and the night blindness [51] seen in catarrhal jaundice or in secondary hepatitis of obstructive jaundice [12] cannot be explained on the basis of disturbed intestinal absorption, since many months are required to deplete the healthy organism of vitamin A.

Clausen and associates [26b] have shown that in certain pathologic conditions (e. g. after ingestion of alcohol) an increased release of vitamin A from the liver into the blood may occur. An indication of such a process was not encountered in our material, although some histologic pictures may well be connected with such an occurrence.

SUMMARY

This study, performed by chemical methods and fluorescence microscopy, is concerned with the comparison between the plasma vitamin A level and the hepatic vitamin A concentration in human subjects under normal and under pathologic conditions.

The plasma vitamin A level showed great variations brought on by varied nutritional intake and by disease. It is moderately reduced in carcinoma of the gastrointestinal tract and greatly reduced in hepatic damage and in jaundice.

Anesthesia has little, if any, influence on the plasma vitamin A level. Comparison between the plasma level and the vitamin A concentration in biopsy specimens of liver over a wide range of the plasma vitamin A level (patients with jaundice, normal patients and patients receiving huge feedings of vitamin A) shows a parallelism between plasma and liver vitamin A concentrations only if the average of a fairly great number of cases is taken. If individual cases are considered no relation between these two factors exists. The plasma vitamin A level is thus no index of the liver stores of the vitamin, except that a high plasma level indicates normal or high stores. In contrast, low plasma levels may be associated with high or low liver contents of vitamin A.

The fluorescence microscopic picture shows great variations of the vitamin A fluorescence pattern. These variations are extremely marked in pathologic conditions of the liver and offer a possibility to recognize hepatic damage morphologi-

47. Moore.[18] Popper.[8b]
48. Soskin, S.: Physiol. Rev. **21**:140, 1941.
49. Murrill, W. A.; Horton, P. B.; Leiberman, E., and Newburgh, L. H.: J. Clin. Investigation **20**:395, 1941. Steininger, Roberts and Brenner.[1e]
50. Lasch, F.: Klin. Wchnschr. **17**:1107, 1938. Breese, B. B., and McCoord, A. B.: J. Pediat. **16**:139, 1940. Lindqvist.[1d]
51. Wohl, M. G., and Feldman, J. B.: Am. J. Digest. Dis. **8**:464, 1941.

cally before it is revealed by routine histologic examination. The disturbance of the pattern is pronounced when there is great discrepancy between plasma and liver concentrations of vitamin A. Since apparently the plasma level is regulated by the liver, these pathologic changes in distribution of vitamin A explain disturbances in the release of the vitamin and the consequent discrepancy. In hepatic disease and in jaundice this disturbed release seems to be common. In general, the plasma level seems a better index for the functional status with regard to vitamin A than do the liver stores.

Intake of huge doses of vitamin A raises the concentration in the plasma and much more that in the liver. This increase is less pronounced in jaundice.

The amount of vitamin A fluorescence as seen under the microscope and the chemical assay for vitamin A (the method of which is discussed) run parallel in the human liver. If high amounts of vitamin A are present, they are chiefly found in Kupffer cells.

CHANGES IN OPTIC FUNCTION AND OPHTHALMOSCOPIC PICTURE

OBSERVED IN FOUR PATIENTS OF THE EUNUCHOID SKELETAL TYPE WHO WERE BEING TREATED WITH AN ORCHIC EXTRACT

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In 1922 Stanley,[1] reporting on implantations of testicular substance, cited greatly strengthened vision in 32 of 41 inmates at San Quentin Prison who had previously complained of poor vision that necessitated glasses.

My interest in orchic extract therapy was aroused by its use in the case of a man who presented the conditions of eunuchoidism and pituitary tumor with changes in the fundi and impairment of optic function. After three months of therapy the ophthalmoscopic picture showed definite improvement. This observation led to the use of this extract in the treatment of 3 other patients of the eunuchoid skeletal type, all of whom were found to have changes in the fundi and impairment of optic function. The serial changes in the ophthalmoscopic picture were observed in the 4 patients so treated, for periods varying from seventeen months to two and one-half years. The cases are reported for their suggestive value and to stimulate collaboration between the ophthalmologist, the internist and the endocrinologist confronted with patients showing similar findings. The patients in cases 1 and 2 present eunuchoidism, while those in cases 3 and 4 present the eunuchoid skeletal disproportions but have normal sex development and function.

REPORT OF CASES

CASE 1.—P. B., a man aged 46, visited the medical clinic of the New York Polyclinic Medical School and Hospital Oct. 31, 1938, where the diagnosis was made of pituitary tumor (chromophobe adenoma or craniopharyngioma) with the syndrome of diabetes insipidus, eunuchoidism, associated hypothyroidism, infection of the tonsils and possible dental infections. He showed genital hypoplasia, a markedly infantile larynx with very short vocal cords. There was no evidence of sinus disease (Dr. W. L. Gatewood). The measurements were: height, 64¼ inches (163 cm.); span, 70¼ inches (178.5 cm.); lower measurement, 37 inches (94 cm.); upper measurement, 27¼ inches (69 cm.). Roentgen examination (Dr. Ernest E. Smith) showed considerable enlargement of the pituitary fossa with destruction of the anterior and posterior clinoid processes on the left side and destruction of the floor of the sella, also a nonhomogeneous focus of calcification in the midportion of the fossa. There was noncalcification of the epiphysial lines of the radius and the ulna. The blood showed secondary anemia, and there was increased tolerance for sugar. The Wassermann reaction of the blood was negative. The basal metabolic rate was minus 23. Examinations of the sputum disclosed no tubercle bacilli.

Report on the Eyes.—The patient had previously visited Dr. Erwin Torok's clinic in 1938 and again on Feb. 8, 1939 for relief of blurred vision. Glasses (convex sphere of 1.50 diopters for each eye) were prescribed for reading but without improvement. On August 18 he still complained of impairment of vision, especially of that of the right eye. Visual acuity then was 20/30 in both eyes. The amplitude of accommodation was 2.75 diopters. The right pupil was irregular and did not dilate after instillation of a solution of homatropine hydrobromide, especially at the outer and upper part. Both pupils reacted promptly to light and accommodation. The optic media were clear. The optic disks were pale with blurred,

From the Medical Clinic of the New York Polyclinic Medical School and Hospital.
1. Stanley, L. L.: Endocrinology **6**:793, 1922.

indistinct margins; the right nerve head was pale, with large physiologic cupping, and the vessels were congested. The impression given was that of postneuritic optic atrophy, especially in the left eye. At this time the visual fields were almost normal for form but extremely contracted for red and green, with a central scotoma for these colors in each eye.

On September 29 (as reported by Dr. Joseph J. Fried, of Dr. Torok's clinic) the decoloration of the nerve heads was more marked. There was no definite blurring of the margin of the right disk, and the nasal half of the disk still showed definite congestion, the lamina cribrosa being very prominent. The left optic disk showed marked blurring along the nasal margin and at the lower half. The visual fields showed bitemporal contraction of about 25 degrees for form and extreme contraction for colors; a central scotoma for red and green was again noted. The color sense test (pseudoisochromatic plates) showed that the patient had difficulty in distinguishing certain shades of red and green. However, he promptly distinguished between red and green (5 and 10 mm. test objects used in determining contraction of visual fields for form; 8 and 12 mm. test objects used in determining contraction of fields for colors). The dark adaptation test (scotopticometer with Tscherning brightness no. 4) gave a result within the normal limits (fig. 2 *A*).

Fig. 1 (case 1).—Roentgenogram of the sella turcica, left.

Additional History.—On November 28 he was admitted for eight days to the Polyclinic Hospital with cerebral concussion resulting from an automobile injury. At this time Dr. Abraham Kaplan, of the department of neurosurgery, reported on the appearance of the fundi as follows: "Bilateral optic atrophy, more on the right. No gross field defects."

Therapy.—On July 13, 1939 hypodermic injections of a solution of an extract of orchic substance were begun. Each cubic centimeter of solution contained 114 mg. of a water-soluble, heat-stable extract derived from 10 Gm. of fresh orchic substance. Glynn [2] has described the preparation of this extract as follows: An acid aqueous extract of bulls' testes is prepared and coagulated by heat to the point of boiling. The precipitate is removed, the filtrate, after concentration in vacuo, is taken up in 70 per cent alcohol, and the precipitate thus formed is filtered off. The 70 per cent alcohol-soluble fraction is evaporated in vacuo to remove the alcohol and precipitated with 4 volumes of acetone. The acetone precipitate is dried and taken up in water to such an extent that 114 mg. is contained in each cubic centimeter and represents the extract derived from 10 Gm. of fresh orchic substance. The solution is filtered until it is clear and sterilized by autoclaving. It is practically free from androgenic substance but contains significant amounts of inhibin. In common with all tissue extracts it contains

2. Glynn, J. H.: Personal communication to the author.

histamine in amounts that are not of therapeutic significance. There has been no assay for vitamin content. McCullagh [3] found that small quantities of this preparation (the orchic extract solution) will cause cessation of the estrous cycle in the normal female rat. He pointed out, however, that this does not necessarily indicate the presence of inhibin. Inhibin will cause cessation of estrous, but so will many other substances. The female rat test is therefore not specific for the hormone.

The first injection of 2 cc. caused syncope and sweating. Subsequent injections were made with doses of from 1 to 2 cc. twice weekly until Aug. 14, 1941. Seven injections of testosterone propionate were substituted during the early part of these studies in order to determine a comparative response. Acetylsalicylic acid and brewers' yeast were given for grip and tonsillitis, which occurred during observation.

Course.—On May 12, 1940 the patient reported improvement in eyesight, stating that he was able to read continuously for several hours, compared with a half hour three months before. Polyuria and polydipsia were much less. He felt subjectively better while under treatment. On Aug. 14, 1941 the injections were discontinued for the purpose of having an examination of the eyes after the lapse of one month without them. On his return he

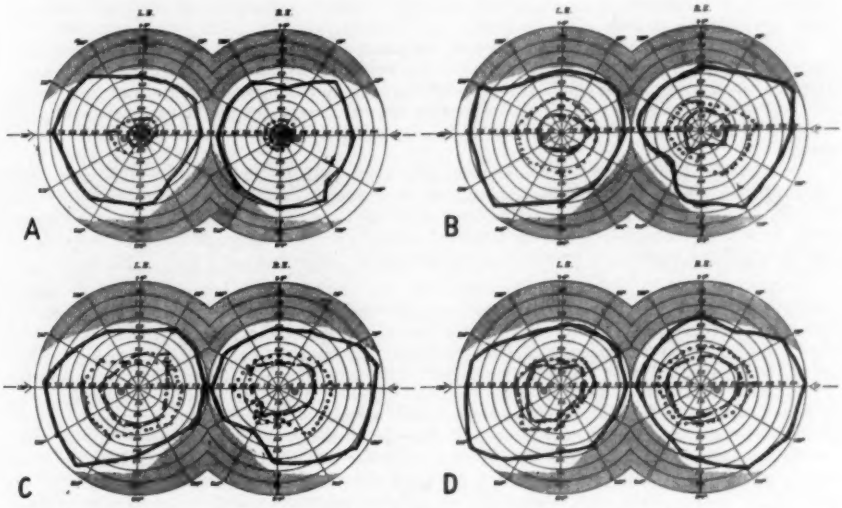

Fig. 2 (case 1).—Charts of the visual fields: *A*, taken Oct. 6, 1939, shows a central scotoma for red and green in each eye; *B*, taken May 11, 1940; *C*, taken Sept. 24, 1940; *D*, taken Sept. 12, 1941.

In these and all the subsequent charts the field limits as determined for form are indicated by a solid line; the field limits as determined for red, by a dotted line; the field limits as determined for green, by a dot-dash line. A central scotoma is indicated by a stippled area. The studies were made with an improved Förster perimeter, 5 mm. test objects being used in determining the fields for form and 8 mm. test objects (except when otherwise stated) in determining the fields for colors at a distance of 330 mm. The illumination used was that from a 75 watt Mazda lamp.

complained of having had weakness and soreness of the legs for three weeks. He was hospitalized at another institution shortly afterward.

Subsequent Examinations of the Eyes (Dr. Joseph Fried).—Because of the presence of a pituitary tumor with the foregoing ophthalmic findings, frequent examinations were made of the visual acuity, accommodative power, fundi, visual fields and dark adaptation. On Dec. 9, 1939 improvement was noted in the ophthalmic picture. The blurring of the disks had now disappeared, but marked bitemporal pallor of both nerve heads, especially of that in the left eye, was still present. The bitemporal crescentic defect for form had diminished,

3. McCullagh, D. R.: Personal communication to the author.

and the color fields had enlarged. No central scotoma was now noted in either eye. Visual acuity was 20/20 in both eyes. (On Aug. 18, 1939 it had been 20/30 in each eye.)

On May 11, 1940 the visual acuity was 20/20 (20/15?) in both eyes (fig. 2 *B*). The amplitude of accommodation had improved from 2.75 to 3.5 diopters. The pupils reacted promptly and dilated well. The fundi were well colored, the margins at the temporal and nasal parts of the disks were well defined and the retinal vessels were normal for the age. The visual fields showed further enlargement for colors as well as lessening of the bitemporal contraction for form.

On June 8, 1940, at a time when the patient had symptoms of grip, both fields showed regression for colors, being then similar to those found on March 6, 1940. By July 22 visual acuity was normal, and accommodative power had increased to 3.75 diopters, corresponding to age 44. The eyegrounds showed nothing abnormal. The visual fields, especially that in the left eye, again showed enlargement for colors as well as lessening of the bitemporal contraction for form.

On September 24 visual acuity was 20/20 (20/15?) in both eyes. There was further increase in accommodative power from 3.75 to 4 diopters (fig. 2 *C*). The fundi were practically within normal limits. One could still trace the paleness of the temporal part of the right disk, the lamina cribrosa being decidedly less prominent. The left eyeground showed no pathologic change. The bitemporal contraction for form had practically disappeared, and for colors the fields were almost normal.

On Sept. 12, 1941, after the omission of treatment for one month, visual acuity with correction was 20/20 in both eyes (fig. 2 *D*); the amplitude of accommodation was 3 diopters (normal for the age); the pupils reacted normally; the fundi showed nothing abnormal except for beginning arteriosclerosis. The fields were normal except for slight contraction for red. Tests with the tangent screen and of dark adaptation and intraocular tension gave normal results.

On Oct. 31, 1940 Dr. Abraham Kaplan, who eleven months before, when the patient had cerebral concussion, reported the findings on examination of the fundi as "bilateral optic atrophy, more on the right; no gross field defects," now reported "Both disks are of good color except for some pallor on the temporal side of the right disk; there is no elevation of the disk, and the vessels are normal in color and caliber."

Case 2.—N. E., a man aged 53, single, had the characteristic features of eunuchoidism; the body was hairless, the penis was small, and the testes were not felt in the scrotum nor the prostate by rectal examination. The larynx was of the infantile type, with short vocal cords; there was no evidence of disease of the sinuses or the tonsils (Dr. W. L. Gatewood). There were several infected teeth. The body measurements were: height 71¾ inches (182 cm.); span, 73 inches (185.5 cm.); upper measurement, 32 inches (76 cm.); lower measurement, 39¾ inches (101 cm.). The blood showed secondary anemia. The Wassermann reaction of the blood was negative. The urine was normal. The basal metabolic rate was minus 12. A roentgenogram showed the sella turcica to be of normal size and shape. On Oct. 6, 1939 the visual fields revealed concentric contraction for form and color. The contraction for form was more marked temporally, especially in the left eye. Diminished visual acuity in the left eye coincided with the field findings. Visual acuity in the right eye was 20/100, with correction 20/20; in the left eye it was 20/70, with correction 20/40. The pupils were very small and oval horizontally.

Examination of the Eyes (Dr. Joseph Fried).—On Dec. 27, 1939 visual acuity was 20/200 in both eyes. A 1.75 convex sphere with a 0.25 convex cylindric lens, axis 180, improved vision to 20/20 in each eye. The amplitude of accommodation was 1 diopter, corresponding to age 60. The addition of convex 3.0 diopter lenses to distance glasses was required for reading of small type (Jaeger 1). The pupils were narrow (2.5 mm.) and reacted promptly to light and accommodation. The retinas appeared pale; the larger retinal vessels were abundant, but the capillaries were very scant. There was marked decoloration of the temporal part of the left disk, with less marked temporal decoloration of the right disk. In the right eye there was enlargement of the physiologic excavation toward the temporal side of the nerve head. The visual fields showed concentric contraction for form and colors (fig. 3 *A*), very markedly temporally. The tangent screen showed no enlargement of the blindspot or any kind of scotoma. The color sense was good; dark adaptation showed nothing abnormal, and there was no increase of intraocular tension.

Therapy.—Injections of the orchic extract were given at the rate of two a week from Oct. 10, 1939 until Dec. 18, 1941, after which they were omitted for seven weeks for a comparative examination of the eyes. During the early period of treatment a substitution of six injections of testosterone propionate in doses varying from 12.5 to 5 mg. was made in order

to note any comparative effect, and several weeks later three injections of chorionic gonadotropin in doses of 100 rat units each were given for the same reason. Brewers' yeast and cod liver oil were ordered for grip and bronchitis when these occurred. After March 19, 1942 several infected dental roots were extracted.

Subsequent Examinations of the Eyes.—On Jan. 15, 1940 definite temporal pallor of each disk was noted. The visual fields showed the same concentric contraction for form and colors, very marked temporally. The tangent screen showed no abnormal changes. The patient had good color sense (Holmgren test). Tests of dark adaptation (scotopticometer Moller) and intraocular tension gave normal results. After March 22 examinations revealed gradual disappearance of the bitemporal pallor of the nerve heads. The papillae became well colored and well defined, and the fundi showed no vascular changes other than those usually found at the age of this patient. The abundance of the capillaries now present was in contrast to their scantiness on Dec. 21, 1939. On March 23, 1940 improvement in the fields was first noted. Thereafter gradual enlargement for white, red and green was recorded. By May 4 visual acuity had improved. Vision then without glasses was 20/100 in both eyes, compared with 20/200 previously; both eyes showed 20/20 with correction. The accommodative power showed considerable improvement. The amplitude of accommodation was 2.5 diopters (compared with 1 diopter on Dec. 22, 1939), and correspondingly weaker lenses were required for near vision. The paleness of the fundi had disappeared, the retinas now having normal coloring. The visual fields were practically normal for form and were almost normal for colors.

On June 8 regression in the fields was noted. At this time the patient was recovering from grip. This proved temporary, for on July 22 the fields again showed improvement for form and colors.

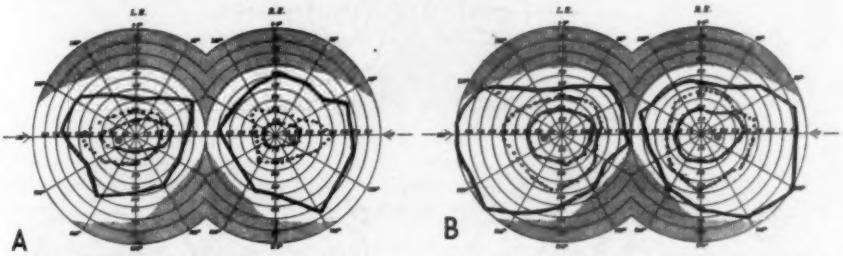

Fig. 3 (case 2).—Charts of the visual fields: *A*, taken Dec. 27, 1939; *B*, taken Sept. 24, 1940. For further explanation of the charts, see the legend for figure 2.

By September 24 the outlines and the color of the disks were quite normal. No abnormal changes were seen in the fundi; the abundance of capillaries were still present. There was normal reaction to light and accommodation. The visual fields (fig. 3 *B*) showed continued improvement, and the outlines at this time almost corresponded with those of May 4. Visual acuity was 20/100 in both eyes and 20/20 with correction. The improvement in the amplitude of accommodation noted on May 4 was still maintained.

On Jan. 3, 1941, visual acuity in the right eye was 20/100; the addition of 2.5 diopters corrected vision to 20/20. The accommodative power was 2.5 diopters. The addition of +2.25 diopter spheric lenses in both eyes enabled him to read the smallest print (Jaeger's test type 1) at 10 inches (25 cm.). The pupils were very narrow (1.5 to 2.0 mm.), and the reaction to light and accommodation was difficult to determine. Under dilatation, the retinas and the choroids appeared normal, the nerve heads were well colored and well outlined, the arteries were undulated, with thickened walls, and the capillaries were abundant. The fields were normal for form and colors. Dark adaptation, the tangent screen, color sense (pseudo-isochromatic plates) and intraocular tension showed no abnormalities.

On Feb. 6, 1942, after omission of treatment since Dec. 18, 1941, examination revealed normal function of the eyes and no signs of pathologic change of the eyegrounds, visual fields or refraction. The amplitude of accommodation continued improved so that weaker lenses (between 1.75 and 2 diopters) were required for reading. The chart of the visual fields corresponded to that of Sept. 24, 1940.

Case 3.—H. J., aged 60, a widower, attended the medical clinic Oct. 17, 1940. He presented eunuchoid skeletal measurements and female distribution of pubic hair but normal sex development and function. He had tertiary syphilis, cerebral arteriosclerosis, with the residuum of a

recent focal lesion in the left temporal lobe which caused impairment of speech, and probably dental infection. The measurements were: height, 65⅞ inches (167 cm.); span, 70 inches (178 cm.); lower measurement, 34 inches (86 cm.); upper measurement, 31⅞ inches (91 cm.); nude weight, 122¾ pounds (55.5 Kg.). Roentgenograms were negative for sinus disease, and the sella turcica appeared normal. The blood count and the urinalysis gave normal results. The figures for blood sugar, uric acid and cholesterol were normal. The Wassermann reaction of the blood was negative with alcohol antigen and 2 plus with cholesterol antigen; the Kahn reaction was 3 plus. The patient would not permit examination of the spinal fluid. The basal metabolic rate was minus 4.

Report on the Eyes (Dr. Joseph Fried).—On Oct. 18, 1940 visual acuity was 20/30 in the right eye and 20/40 (?) in the left eye. As to near vision, he was able to read Jaeger's test type 3 with the right eye and Jaeger's test type 5 with the left. Vision could not be improved by adding lenses. The amplitude of accommodation was 0.25 diopter, corresponding to an age of about 65 years. Motor function of the eyeballs was fairly good, and the optic media were clear. Both eyegrounds showed pale, decolored, whitish gray optic disks with ill defined and blurred margins, especially the left eyeground temporally. There was no pathologic change in the choroid, the retina or the retinal vessels in either eye. The visual fields showed concentric

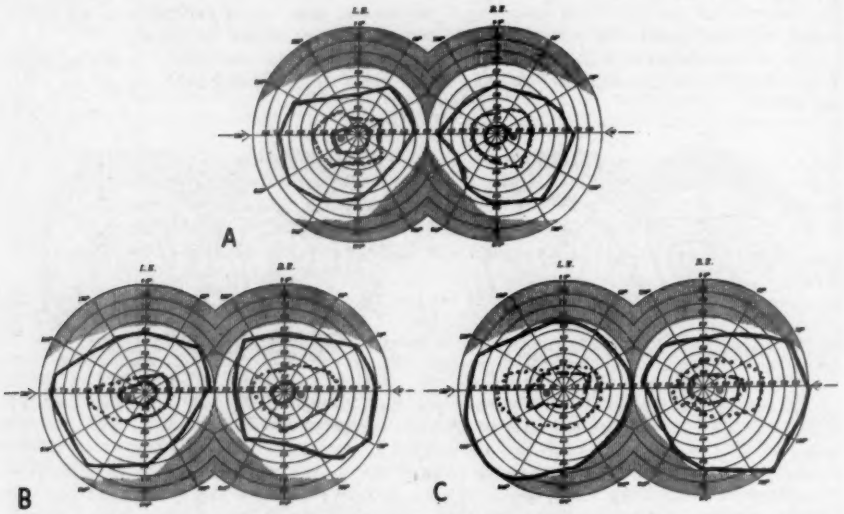

Fig. 4 (case 3).—Charts of the visual fields: *A*, taken Oct. 23, 1940 (10 mm. test object used in determining fields for colors); *B*, taken March 15, 1941; *C*, taken Oct. 6, 1941 and Feb. 5, 1942 (10 mm. test object used in determining fields for colors). For further explanation of the charts, see the legend for figure 2.

contraction for form and color (fig. 4 *A*), and there was decreased dark adaptation (six minutes with Moller's scotopticometer). At this time a diagnosis of bilateral optic atrophy was made, but there was doubt as to whether this was due to arteriosclerosis, syphilis or post-neuritic atrophy of the optic nerve.

Therapy.—The patient had received antisyphilitic treatment for two and one-half years. On Nov. 11, 1940, two months after antisyphilitic treatment had been suspended, injections of orchic extract were begun. Doses varying from 2 to 0.5 cc. were given twice weekly until Feb. 16, 1942. The treatment was then discontinued in order that the eyes might be examined after two months' omission of treatment. On January 6 he was referred to the dermatology clinic (Dr. Jerome Kingsbury), where weekly injections of a bismuth preparation were started.

Course.—The patient felt stronger during the treatment with orchic extract. Three months after treatment with the extract had started, at a time when he had a cold, a change appeared at the temporal side of the left eye suggesting bluish smoke with occasional threads like soot in front of it. This has occurred about six times during the past five years. When it recurred

on March 10, 1941 he was referred to the ophthalmology clinic. (See examination of the eyes of March 15, 1941). On June 24 he had the first of several dental extractions, but he still retains a gold-capped tooth.

Subsequent Examination of the Eyes (Dr. Joseph J. Fried).—On Nov. 27, 1940 decoloration of both optic nerves was still present. Visual acuity was 20/30 in the right eye and 20/40—$\phi 2$ in the left eye; there was some enlargement for green in the visual fields as compared with the finding on Oct. 18, 1940.

On December 30 vision was 20/20 —$\hat{2}$ in the right eye and 20/25 —2 in the left eye, and 20/25 with correction; the near point was 530 mm. for each eye; the right pupil measured 6 mm.; the left, 7 mm.; the right pupil was irregular, and there was poor response to light and accommodation. The fields were almost normal for form; there was still concentric contraction for red and green. The disks were now well colored and well outlined.

On Feb. 28, 1941 visual acuity was improved. The right eye was 20/20; the left eye was 20/25. Near vision (reading of Jaeger's 1 test type) was obtained with + 3.5 diopters for both eyes. The pupils were the same size as on Dec. 30, 1940, and both reacted fairly well. The nerve heads now appeared well colored and well outlined; there was a peripapillary choroidal atrophy at the temporal margin of the left disk. The retina, the choroid and the retinal vessels in each eye were normal. The dark adaptation was normal at this time (three minutes). The visual fields showed improvement for form but not for colors. There was a striking change in the appearance of the fundi as compared with their appearance on Oct. 18, 1940.

On March 15, 1941, five days after the recurrence of the bluish smoke in the temporal part of the left eye, the left disk appeared paler than at the previous examination, the temporal margins of the disks were ill defined and there was peripapillary edema of the retina (fig. 4 *B*). Vision in the right eye was 20/30; vision in the left eye, 20/50, improved with glasses to 20/25. One week later the peripapillary retinal edema and blurring of the temporal margins had disappeared, and visual acuity in the left eye was 20/30 without correction.

On October 6 the first positive enlargement of the visual fields for color was noted. Visual acuity was 20/20 in each eye with correction. The amplitude of accommodation corresponded to the age of the patient. Near vision (reading of Jaeger's test type 1) was obtained with + 3.5 diopters in both eyes. The optic disks were well colored and well defined. No pathologic change was seen in the retina, and there were no signs of arteriosclerosis. The arterioles were distinctly seen. There were no corkscrew maculopapillary venules. The dark adaptation was normal. The visual fields were normal for form; their contraction for colors was diminished (fig. 4 *C*).

On Feb. 5, 1942 vision in each eye was 20/20 with correction and reading of Jaeger's test type 1 (near reading) was obtained with + 3.5 diopters. The eyegrounds were normal. The visual fields were almost normal for form (fig. 4 *C*). For colors, though improved, they were still narrower than normal. The findings on April 16 corresponded to those of February 5. He had received no injections of orchic extract between these dates. Injections of a bismuth preparation were begun on Jan. 6, 1942.

Case 4.—R. E., aged 42, married, an attorney, during a regular visit with his son, a pituitary dwarf, became emotionally upset while relating his financial reverses. His depressed spirits prompted the injection of orchic extract. A week later casual questioning elicited the unexpected report that he had noticed perceptible clearing of the head and decided clearing of vision, especially for street lights, while driving home after the injection the week before. The same evening he was able to read printed matter without glasses. He had never experienced this before. He was also relieved of a quite constant pressure over the eyes and lower part of the forehead which had troubled him for several years. On this information he was referred for an examination of the eyes. (See report for Dec. 11, 1940.) His parents are related as cousins. Several brothers are over 6 feet (183 cm.) tall. He had the typical eunuchoid skeletal measurements and female distribution of the pubic hair but normal sex development and function. The measurements were: height, 71⅝ inches (182 cm.); span, 74 inches (188 cm.); lower measurement, 38 inches (96.5 cm.); upper measurement, 33⅝ inches (85.5 cm.); nude weight, 173¼ pounds (78.6 Kg.). The heart was slightly enlarged to the left; the sounds were normal. Roentgenograms showed the sella turcica larger than average but otherwise normal. There was no evidence of sinusitis. The frontal sinuses were considerably larger than average, and pneumatization of the ethmoid cells was more pronounced. The blood count and the differential percentages were normal. The blood sugar amounted to 105 mg., uric acid to 4 mg. and cholesterol to 160 mg. per hundred cubic centimeters. The urine had a faint trace of albumin and a specific gravity of 1.032 but was otherwise normal. The Wassermann reaction of the blood was negative. The basal metabolic rate was minus 5.

Report on the Eyes (Dr. Joseph J. Fried).—On Dec. 11, 1940 examination showed wide palpebral fissures (12 mm.). The oculomotor apparatus was intact. Arcus senilis was present in both eyes. There was prompt pupillary response. Both disks showed slight pallor, the right more than the left; the arteries were markedly narrowed, with signs of premature sclerosis. Hypermetropic astigmatism was present. Visual acuity was 20/40 in both eyes without correction and 20/20 with correction. The amplitude of accommodation was 2 diopters, corresponding to the age of 54 years. The visual fields were normal for form and slightly contracted for colors; there were central scotomas for red (fig. 5*A*). The tangent screen showed a 7 degree downward enlargement of the blindspots.

Therapy.—The patient was given six injections between Dec. 3 and 31, 1940, when the eyes were reexamined. A total of twenty injections was given in the seventeen months that followed.

Course.—Two weeks after treatment had started he could read without the glasses which had been required for several years. Vision in daylight had improved considerably. He felt more alert. Further injections gave complete relief from the feeling of pressure and fulness between the eyes and in the frontal region. After February 1941 he had had several attacks of grip and received treatment at infrequent intervals. His consumption of tobacco was unchanged.

Subsequent Examinations of the Eyes (Dr. Joseph Fried).—On Dec. 31, 1940 visual acuity for distance was unchanged but there was improvement in near vision. He read medium-sized newspaper print (Jaeger test type 3) without glasses. At the first examination (December 11) he required the addition of convex 2.5 diopter lenses to read Jaeger's test type 1 at a dis-

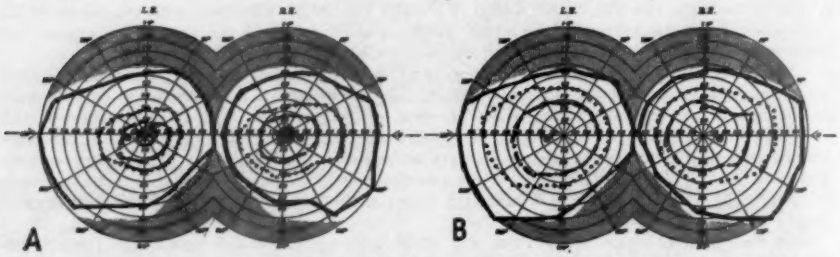

Fig. 5 (case 4).—Charts of the visual fields: *A*, taken Dec. 11, 1940; *B*, taken Oct. 23, 1941. For further explanation of the charts, see the legend for figure 2.

tance of 200 mm. At the later examination the addition of convex 1.75 diopter lenses to distance-correcting lenses enabled him to read Jaeger's test type 1. The amplitude of accommodation had improved from 2 to 2.5 diopters. The paleness of the right disk previously observed was not present. The enlargement of the blindspot in the right eye diminished to the normal limits.

On Feb. 18, 1941 the same glasses were suitable for distance that were suitable on Dec. 11, 1940. He read without lenses newspaper print at 540 mm. distance with the right eye and at 410 mm. distance with the left. Using street glasses, he read the smallest print of the test chart for near reading at 400 mm. with each eye. The addition of convex 1.5 diopter lenses to the distance lenses enabled him to read the smallest print at 200 mm. The amplitude of accommodation (2.75 diopters) corresponded to the age of 47 to 49 years. There was normal oculomotor balance for distance and near. There was a return of the slight pallor of the right nerve head, present at the initial examination on Dec. 11, 1940 but absent on Dec. 31, 1940. The visual fields and tangent screen tests did not show the central scotoma for color and the enlarged blindspots noted at the first examination. The amplitude of accommodation was the same as on Dec. 31, 1940. (The patient was recovering from grip at the time of this examination.)

On Oct. 23, 1941 the palpebral fissures were of normal width (10 mm.). The optic disks were well colored and well defined, and the retina and the choroid were of normal appearance. However, the arteries were narrower than normal. The visual fields and the findings with the tangent screen were normal (fig. 5*B*). There were no central scotomas for color or enlargement of the blindspots. The visual acuity showed decided improvement. Distance vision without glasses was 20/20 in both eyes, and the amplitude of accommodation was 4.5 diopters, corresponding to age 40, so that the reading glasses previously used were not necessary for

close work. (He had not received orchic extract from March 19 to Oct. 14, 1941 and at the latter date was recovering from another cold.)

By Feb. 25, 1942 the patient, who had received but one injection of orchic extract in over eleven months (that on Oct. 14, 1941), showed visual acuity for distance unchanged. However, the amplitude of accommodation was 2.5 diopters, there was slight enlargement of the blindspot in each eye, and the fields were narrower for colors than on Oct. 23, 1941.

On April 6, 1942, visual acuity in each eye was 20/20 with correction, and the amplitude of accommodation measured between 2.75 and 3.0 diopters. The eyegrounds showed no pathologic change. However, the blindspots were still slightly enlarged (4 degrees downward), and the visual fields were somewhat narrower for red and green than on Oct. 23, 1941. (By April 6, 1942 he was recovering from six weeks of grip and had received but one injection of orchic extract in more than a year.)

COMMENT

These patients were treated with injections of the orchic extract for periods varying from seventeen months to two and one-half years. An occasional complaint was made of pain at the site of injection, but there were no untoward symptoms with doses below 2 cc. This dose caused syncope in 1 patient. The dose of 1 cc. seemed ample.

The addition of acetylsalicylic acid, brewers' yeast and cod liver oil occasioned by grip and tonsillitis, which arose during the periods of study, can in no way be responsible for the favorable ocular changes noted. In fact, examinations of the eyes made during convalescence from grip showed decreased visual acuity for distance and marked impairment of the amplitude of accommodation without pathologic change in the eyegrounds; also, the visual fields were noticeably contracted for form and color compared with those found prior to and subsequent to the intercurrent ailment. Removal of dental infections when present was not begun until the treatment with orchic extract was well advanced and definite ocular improvement had occurred.

One was impressed by a greater sexual stimulus after each injection of testosterone propionate, compared with a better subjective response after an injection of orchic extract, though the limited number of injections does not permit an appraisal of any effect on the ophthalmoscopic picture.

The studies of the visual fields were made with an improved Förster Perimeter, 5 mm. test objects being used in determining contraction of the fields for form and 8 mm. test objects in determining contraction of the fields for colors (except when otherwise stated) at a distance of 330 mm. The tangent screen studies were made on a Gruss tangent screen with 4 mm. and 2 mm. test objects at a distance of 1 meter; the illumination used was that from a 75 watt Mazda lamp.

SUMMARY

Observations on 4 patients having eunuchoid skeletal measurements, one of them with eunuchoidism, another with eunuchoidism and a pituitary tumor, treated with injections of an orchic extract showed subjective improvement with a feeling of well-being and loss of fatigue. Before treatment all showed decreased visual acuity of more or less marked degree and diminished amplitude of accommodation. The eyegrounds showed changes ranging from hyperemia and postneuritic signs to complete decoloration of the optic nerve heads. Usually some vascular disease was present either in the form of premature arteriosclerosis or in that of absence of arterioles and capillaries. The visual fields were contracted, especially for colors (red and green), and in 2 cases there were central scotomas for colors. Usually there was diminished dark adaptation. During this therapy definite improvement was noted in the visual acuity for distance and in the amplitude of accommodation.

The pathologic changes in the eyegrounds disappeared, and later these showed normal, well colored and well defined optic nerve heads with little or no vascular abnormality. Dark adaptation returned to normal. The contraction of the visual fields for form and colors was definitely reduced, in some cases to normal.

Encouragement to publish the limited number of cases has come through some improvement with this therapy already noted in 3 other patients who have been observed from two to four months, an insufficient period for a report. The conditions treated have been (1) genuine syphilitic atrophy of the optic nerve, (2) optic atrophy associated with a pituitary adenoma and (3) retinitis pigmentosa.

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Dr. Ervin Torok's ophthalmologic clinic cooperated in this work, especially Dr. Joseph J. Fried of Dr. Torok's staff, who made numerous ophthalmologic examinations and collaborated extensively; Dr. A. Sumner Price, director of the laboratory; the consultants quoted and Drs. N. B. Martin, Barnard Robbins, Antoinette Raia and Franklin V. Sunderland gave helpful cooperation in the medical clinic.

ACQUIRED HEMOLYTIC ANEMIA

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The anemia produced by accelerated disintegration of red blood cells leading to jaundice, increased excretion of urobilinogen and moderate splenomegaly often is accompanied by morphologic alterations of the red cells and usually is classified as hemolytic anemia. In a few instances the process may be truly hemolytic in the strict meaning of the word. However, in a majority neither the mechanism of the destruction of the red cell nor the fate of its stroma is known. I shall therefore employ the word "hemolysis" in its loose, hematologic rather than in its narrower, immunologic meaning throughout this discussion unless a clear distinction is specified.

I have observed a number of patients presenting hemolytic icterus of unknown cause with an acute or a subacute course similar to those whose cases were reported earlier by Widal and by Chauffard and their associates. In addition I have records of a number of patients with chronic acquired hemolytic anemia of unknown cause whose disease began acutely and followed a course characterized by continuous increased hemolysis and by recurrent severe crises of hemolysis similar to those seen in acute acquired hemolytic anemia.

Acute hemolytic anemia probably was first reported by Mackintosh and Cleland[1] in 1902. A few years later it was accurately described by Widal, Abrami and Brulé[2] and was given the name "acquired hemolytic icterus" to differentiate it from the congenital type of hemolytic icterus, which had been described accurately by Minkowski[3] a few years earlier. Chauffard[4] had discovered the diminished osmotic resistance of the red cells and also the lessened diameter of the erythrocytes in congenital hemolytic anemia a short time before Widal's studies of acquired hemolytic icterus were published. Widal, Abrami and Brulé[5] a year later reported autoagglutination of the red cells in the acquired type of the disease. Chauffard and Troisier[6] also studied the blood of a patient with the acute type of acquired hemolytic anemia and found that the serum contained an isohemolysin for normal erythrocytes. They, therefore, gave the name "acute hemolysinic anemia" to the malady. During the years between 1907 and 1915 a number of discussions of acquired hemolytic anemia appeared in the French medical journals. Brulé[7] in 1922 reviewed the whole subject up to that date and pointed out

1. Mackintosh and Cleland, cited by Sterner, L. G.: Ein Fall von akuter hämolytischer Anämie von Ledererschen Typ, Acta pædiat. **28**:196, 1940.

2. Widal, F.; Abrami, P., and Brulé, M.: Differenciation de divers types d' ictéres hémolytiques par le procédé des hématies deplasmatisées, Presse méd. **15**:641, 1907.

3. Minkowski, O.: Ueber eine hereditäre, unter dem Bilde eines chronischer Ikterus mit Urobilinurie, Splenomegalie und Nierensiderosis verlaufende Affection, Verhandl. d. Kong. f. inn. Med. **18**:316, 1900.

4. Chauffard, M. A.: Pathogénie de l'ictére congénital de l'aduite, Semana méd. **27**:25, 1907.

5. Widal, F.; Abrami, P., and Brulé, M.: L'autoagglutination des hématies dans l'ictère hémolytique acquis, Compt. rend. Soc. de biol. **64**:655, 1908.

6. Chauffard, M. A., and Troisier, J.: Anémie grave avec hémolysine dans la sérum; ictére hémolytique, Semana méd. **28**:94, 1908.

7. Brulé, M.: Recherches sur les ictéres, Paris, Masson & Cie, 1922.

the confusion which had resulted from the frequent failure to differentiate between hemolytic icterus with anemia and icterus of other types with anemia. Widal and Abrami [8] in 1928 summarized the earlier reports and recorded their views concerning the mechanism of the disease. It is of interest that they did not seem to be aware of the presence of normal agglutinins and agglutinogens in human blood at that time. Thus there was some doubt concerning the significance of the autoantibodies and isoantibodies in the serum of the patients observed earlier by Widal, Abrami and Brulé [5] and by Chauffard and Troisier [6] until the results of later studies fortunately confirmed their original observations.

I observed a patient with acute hemolytic anemia in 1916 and made a diagnosis of acquired hemolytic icterus. The patient recovered after splenectomy. Although the resistance of the red cells was normal, no studies to demonstrate autoantibodies in the blood of that patient were made.

In 1922 Eppinger [9] presented a summary of his studies of hemolytic anemia. He reported in detail 4 cases of acute hemolytic anemia which he had observed. Each of the patients was cured by splenectomy. All of them had increased hypotonic fragility of the red cells, and each was operated on while the anemia was profound. Eppinger discussed the problem of autoantibodies and isoantibodies but, apparently, was skeptical of the importance of these in the genesis of the malady, although he stated he had made no studies to determine their presence in his patients. The disease was reported by Lederer [10] and by Moschcowitz [11] in 1925. Neither of these authors seemed to be aware of the extensive literature on acquired hemolytic anemia. Davidson [12] in 1932 and Giordano and Blum [13] as late as 1937 described, as a new feature, the phenomenon of autoagglutination in this disease.

Meulengracht [14] discussed the disease briefly in 1938. He was aware of Eppinger's [9] report, but he did not mention the disease as Lederer's anemia. He was of the opinion that acute hemolytic anemia was of varied causation and not a true disease entity, and therefore he did not discuss the disease fully.

The recent report by Dameshek and Schwartz [15] contained a review of the reported examples of acute hemolytic anemia and an attempt to elucidate the importance of the hematologic phenomena in accordance with their experimental and clinical observations. They were able to find references to about 100 cases of acquired hemolytic anemia of varied causation which had been reported since 1907 under an array of different names. Their article contained an extensive bibliography, a comprehensive summary of the clinical and hematologic features of the disease and a discussion as to the proper nomenclature.

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8. Widal, F., and Abrami, P.: Les ictéres, in Nouveau traité de médicine, Paris, Masson & Cie, 1928, vol. 16, p. 263.

9. Eppinger, H.: Die hepato-lienalen Erkrankungen, in Langstein, L., and others: Enzyklopaedie der klinischen Medizin, Berlin, Julius Springer, 1920.

10. Lederer, M.: A Form of Acute Hemolytic Anemia Probably of Infectious Origin, Am. J. M. Sc. **170**:500, 1925.

11. Moschcowitz, E.: An Acute Febrile Pleiochromic Anemia with Hyaline Thrombosis of the Terminal Arterioles and Capillaries, Arch. Int. Med. **36**:89 (July) 1925.

12. Davidson, L. S. P.: Macrocytic Haemolytic Anemia, Quart. J. Med. **25**:543, 1932.

13. Giordano, A. S., and Blum, L. L.: Acute Hemolytic Anemia (Lederer's Type), Am. J. M. Sc. **193**:786, 1937.

14. Meulengracht, E.: Acquired Hemolytic Jaundice, in Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938, p. 2314.

15. Dameshek, W., and Schwartz, S. O.: Acute Hemolytic Anemia (Acquired Hemolytic Icterus, Acute Type), Medicine **19**:231, 1940.

They preferred the designation "acute hemolytic anemia" to the name "acquired hemolytic icterus" first used by Widal. I have followed their nomenclature at times in this paper simply to avoid confusion. However, I am convinced that a chronic type of the disease, and a recurrent form also, occurs more frequently than has been reported and therefore that the name "acquired hemolytic icterus" should be retained, with the terms "acute" and "chronic," as the better designation of the disease.

The 12 patients whose histories I am recording at this time were observed subsequent to 1916. Since I was, at that date, familiar with the reports of Widal and Chauffard, it is not likely that I failed to recognize the disease when I observed it. Thus I believe the disease is of relatively rare occurrence.

REPORT OF CASES

CASE 1.—A woman about 25 years of age entered the Johns Hopkins Hospital, in Baltimore, in the spring of 1916, complaining of weakness. She had been losing strength for several weeks and had become very pale. Her previous history and the family history were unimportant. No other member of her family had had a similar disease.

At physical examination there was fever with a temperature above 102 F., as well as extreme pallor and deep jaundice. The spleen was slightly enlarged.

The hemoglobin content was about 30 per cent, and the erythrocyte count was 1,750,000 per cubic millimeter. There was moderate leukocytosis. The urine contained bile and increased amounts of urobilinogen. The osmotic resistance of the erythrocytes was normal. There was, at that time, some doubt as to whether the patient had a hemolytic crisis in the course of congenital hemolytic icterus or had acquired hemolytic icterus.

Her condition did not improve after several transfusions. Soon a series of convulsions developed. Her condition became critical, and as a last resort the spleen was removed. About the tenth day she began to have fever again. An abscess under the left side of the diaphragm was opened and drained. The patient eventually recovered completely.

Her blood contained dark-staining microcytes which we would now call spherocytes, although at that time they were classed simply as microcytes.

CASE 2.—C. M., a white girl of 15 years, was first seen on May 7, 1934. She complained of blotching of the skin, chiefly over the arms and legs, of three months' duration. These blotches were irregular and purplish red and usually followed fatigue or exposure to cold. They appeared from one to a dozen times a day.

Her past history was irrelevant, except that she had seasonal hay fever. Menstruation had begun a year previously, and the interval and the amount of flow were irregular.

Her father had advanced otosclerosis, and her mother had asthma and hay fever. There were no siblings and no history of anemia in the family.

Physical examination showed the girl to be normal except for the cutaneous manifestations mentioned.

About two weeks later, the blotching of the skin was more marked, and she complained of fatigue and extreme sensitivity to cold. At this time the peculiar dappled blotching of the skin was pronounced over the face, neck, arms and legs. Her temperature was 99.2 F. The results of physical examination were again negative. The skin regained its normal appearance after the patient had remained a short time in a warm room.

On May 22 the urinalysis gave normal results. The hemoglobin content was 57 per cent. The erythrocyte count was 2,520,000. The leukocyte count was 9,150. The stained smear was normal except for hypochromia and slight anisocytosis. From this time on there was constant fever, the temperature usually reaching 102 F. daily. There was also increasing prostration.

On June 2 the right ear became painful, and a few drops of serous fluid were obtained by myringotomy. The erythrocyte count was 3,200,000. The hemoglobin content was 59 per cent, and the leukocyte count was 12,500. The icteric index was 8. The platelet count was 165,000 per cubic millimeter. Agglutination tests for typhoid-paratyphoid and Malta fevers were negative.

On June 4 the stools were dark, and the urine was coffee colored but contained no hemoglobin. There were gastrointestinal distress, occasional vomiting and tympanites.

On June 6 there was no occult blood in the stools. The hemoglobin content was 43 per cent. The erythrocytes were not abnormally fragile; hemolysis began in a 0.48 per cent

saline solution and was complete in a 0.34 per cent solution. The reticulocyte count was 1.2 per cent. A blood culture taken five days earlier was negative.

On June 8 the hemoglobin content was 31 per cent, the erythrocyte count was 1,310,000 and the leukocyte count was 14,800, with neutrophils 58 per cent, lymphocytes 35 per cent and the remainder normally distributed. The icteric index was 22.8. The Wassermann reaction was negative. The clotting time of the blood was eight minutes. The urine contained a heavy trace of albumin and a few hyaline casts but no bile. The temperature was 104.6 F. The pulse rate was 120 and the respirations were 30 per minute. The skin and scleras were markedly icteric. There were no petechiae. The gums and the throat were normal. The lymph nodes were not enlarged. A loud systolic murmur was heard at the cardiac apex. The spleen and the liver were not felt. The patient's blood belonged to group II (AB). Her blood contained an autoagglutinin to her own erythrocytes and to all cells of group II. Her serum did not agglutinate her father's erythrocytes, and his blood was of group IV. She was given 500 cc. of his blood without reaction. She seemed better the next day, but her fever remained high.

On June 10 the hemoglobin content was 30 per cent, and the erythrocyte count was 1,400,000. One drop of the patient's venous blood was placed in 2 cc. of 1 per cent citrate solution and shaken. Hanging-drop preparations of this blood specimen showed rapid and marked autoagglutination. The patient's blood serum on this date also agglutinated her father's erythrocytes (group IV [O]) in fifteen minutes and also group IV (O) cells from 2 normal persons and group II (AB) cells from a normal person. No autohemolysins were present. Stained smears of the blood showed numerous spherocytes and macrocytes and a few normoblasts.

The patient died on June 12. Her temperature reached 106 F. by axilla, and her pulse and respirations became very rapid before death.

Autopsy.—(The embalmed tissue was not placed in fixing solution for several days, so that the stained microscopic sections were not very satisfactory.) The liver weighed 1,800 Gm. The cut surface had a coarse granular appearance. The parenchyma was firm and dark red.

The spleen weighed 240 Gm. It was dark red and firm. The cut surface was granular and cut with a grating sensation.

There were marked gross changes of all lymph nodes of the abdominal cavity. These nodes were very firm and dark red. There was a cluster of nodes, varying in size from a walnut to a pea, located at the hilus of the spleen. A similar cluster of nodes was located about the celiac plexus. The cut surfaces of these nodes had the appearance of normal liver tissue, thus resembling hemolymph nodes. About two hundred of these nodes were scattered through the mesentery and the retroperitoneal areas. The mediastinal and superficial lymph nodes were unchanged.

The chief alterations observed in sections of the spleen were diffuse congestion of the pulp spaces with moderate compression of the blood sinuses. The majority of the sinuses were empty and lined with large endothelial cells. A number of these endothelial cells contained varying amounts of hemosiderin. The malpighian corpuscles were less numerous than normal.

The enlarged lymph nodes found in the mesentery all exhibited greatly widened sinuses, which were filled with lymphocytes and macrocytes.

Sections of the kidneys showed enlarged glomeruli, with partial occlusion of the capillaries by swollen endothelial cells.

The liver showed small areas of necrosis.

Case 3.—E. A., a white married woman 45 years of age, was admitted to Saint Mary's Long Beach Hospital, Long Beach, Calif., on July 22, 1940 and died on Aug. 30, 1940.

Her illness began about four days before admission with pain in the epigastrium and on the right side of the back over the lower ribs. The pains continued, and two days later she vomited and was found to have fever.

The past history was irrelevant. So far as she knew, no member of her family had had a similar illness or chronic jaundice.

She was pale and icteric. The skin was otherwise normal. The throat and the gums were normal. The scleras were icteric. The lymph nodes were not enlarged. There was a soft systolic murmur over the heart. The abdomen was not tender, and no masses or viscera were felt. On July 22 the Wassermann and Kahn reactions were normal. The hemoglobin content was 16 per cent. The erythrocyte count was 795,000, and the leukocyte count was 35,600 (not corrected for normoblasts). There were 74 per cent neutrophils, and the proportion of the other cells was normal. There was anisocytosis with macrocytes and microspherocytes and many diffusely basophilic erythrocytes. Many normoblasts were present. The icteric index was 25.

The fever remained between 101 and 104 F., and from her admission until August 16 she received eleven transfusions. Following each of these, the fever became higher and the icterus more pronounced. On July 29, the erythrocyte count was 2,080,000, the leukocyte count was 14,600 and the hemoglobin content was 25 per cent.

The fragility of the erythrocytes was normal (initial hemolysis at 0.46 per cent and complete hemolysis at 0.32 per cent) on several occasions. The patient's blood belonged to group O. No autoagglutinins, autohemolysins, isoagglutinins or isohemolysins were demonstrated at room temperature, although isoagglutinins and autoagglutinins were present when the blood was in the ice box.

The urine and the stool contained bile.

The spleen was removed August 16. It weighed 510 Gm. After this operation the patient improved rapidly. On August 21 the hemoglobin content was 52 per cent, and the erythrocyte count was 3,140,000. A few days later, chills and fever developed, and the patient failed rapidly. She died on August 30.

Autopsy (Aug. 30, 1940).—An abscess containing about 75 cc. of pus was present below the left side of the diaphragm. Adhesions were present about the gallbladder and adjacent viscera. The liver was moderately enlarged and firm. The bone marrow and the lymph nodes were normal.

The spleen (removed at operation) weighed 510 Gm. The organ was firm and was normal in shape. It was grayish purple. Its cut surfaces were dark red with prominent, irregularly shaped grayish foci, less than 1 mm. in diameter, representing accentuated normal architectural markings.

On microscopic examination the splenic follicles were small and distinct, with no evidence of fibrosis. The sinusoids were almost empty and were prominent, their endothelial cells being large. Hyperplasia of the reticular system was marked. There was congestion of the pulp, but there was noticeable destruction of red blood cells, many disintegrating red cells being present and much amorphous debris being found. There was no evidence of leukemia.

Case 4.—M. S., a white woman 27 years old, was admitted to the Cedars of Lebanon Hospital, in Los Angeles, on Jan. 11, 1941 and was discharged on Feb. 10, 1941.

In July 1940 she had on her arms and legs a few areas that looked like blisters. The larger ones were about 3 cm. in diameter. These broke and discharged and then disappeared and have not recurred. At that time she was given a few doses of a sulfonamide compound, and she thinks she became anemic. In October 1940 she was told that her blood counts were normal, and she felt well. About two weeks before admission she had headaches and became weak. She could not walk without staggering. She had pounding in her ears on the least exertion. A few days later she noticed that her skin was yellow. During this time she took no medicine except a few tablets of acetylsalicylic acid.

At examination, the temperature was 101 F., the pulse rate was 100 and the blood pressure was 105 systolic and 55 diastolic. She was pale, and the skin and the scleras were moderately icteric. There were no petechiae. The mucous membranes were normal except for pallor. The lymph nodes were not enlarged. The spleen was easily felt. The liver was not enlarged.

The urine was normal and contained no bile. Urobilinogen was present (1:100). The icteric index was 54. The erythrocyte count was 1,480,000. The hemoglobin content was 26 per cent and the leukocyte count was 5,100. There were 77.5 per cent neutrophils and 20.5 per cent lymphocytes. There was moderate anisocytosis. No spherocytes were seen. There were numerous normoblasts. The fragility of the erythrocytes to hypotonic salt solutions was normal; hemolysis began at 0.45 per cent and was complete at 0.3 per cent. The gastric analysis showed 35 per cent free hydrochloric acid and 65 per cent total acidity. The bleeding time (Duke method) was two minutes and thirty seconds. The Wassermann reaction with serum was negative. The blood did not show the bands of a porphyrin. The patient's blood belonged to group AB. The serum produced no hemolysis or agglutination when set up with the patient's own erythrocytes either in the ice box or at room temperature. There was also no hemolysis at 80 C. with any normal type serums used against the patient's cells. Furthermore, heated normal serums reactivated with guinea pig complement against her cells produced no hemolysis. The serums of groups B and O and cells of the patient showed hemolysis and strong agglutination.

In the hospital the patient's temperature varied from 101 to 106 F. She was gravely ill, and in spite of numerous transfusions her condition did not improve. The hemoglobin content reached 50 per cent before operation. On Jan. 20, 1941 the spleen was removed. Just after the operation the platelet count was 330,000 per cubic millimeter. Her temperature reached normal two days after operation.

On January 22 the hemoglobin content was 60 per cent, and the leukocyte count was 10,000. On January 31 the patient aborted a 2 month fetus. She was given three transfusions after operation, and her condition slowly improved, although mild blood changes were still present in August 1942.

The spleen measured 15 by 7 by 4 cm. At the hilus were several small accessory spleens. The veins were thin and smooth. The cut surface was fleshy and deep purple. Scattered through the pulp were numerous small nodules, irregular in shape and size but slightly larger than malpighian bodies, and measuring up to 3 mm. in diameter. The gross specimen was reminiscent of a spleen showing Hodgkin's disease.

The microscopic observations on the spleen were as follows: The capsule was normal. The trabeculae were normal. The blood vessels were dilated, and there were a few intravascular thrombi. The pulp spaces showed unusually dilated sinusoids, giving the impression of intense, fairly acute and active hyperemia. The distinction between sinusoids and pulp was poorly defined, and in the pulp there was moderate reticuloendothelial hyperplasia. The majority of the follicles were normal. Some were altered to form the gray nodules seen in the gross specimen. These showed hyperplasia and infiltration with lymphocytes, polymorphonuclear cells and a few plasma cells. There were a few multinucleated cells in the areas of newly formed stroma. There were a few hemorrhages near the follicles. There was little erythrophagocytosis. Splenic extracts were made, but no hemolysin was demonstrated. Stains of the spleen for iron showed a large increase.

CASE 5.—J. B., a white woman 32 years old, was admitted to Saint Mary's Long Beach Hospital, Long Beach, Calif., on Feb. 10, 1942 and died on Feb. 14, 1942.

She had had heart trouble for many years. The acute illness for which she was admitted to the hospital began ten days previously with generalized pains and fever. There was also considerable cough at first. During the illness the urine was dark. During the past twenty-four hours the skin had become yellow.

There were pallor and moderate icterus. There were no petechiae and no enlarged lymph nodes. The pulse rate was 110 per minute. The temperature was 101 F. The blood pressure was 120 systolic and 60 diastolic. There were sibilant rales in each lung. The heart was enlarged to the right and to the left. The first sound was loud at the apex, and there were a loud presystolic murmur and a short, loud systolic murmur. The edge of the liver was 4 cm. below the left costal margin.

On February 11 the hemoglobin content was 7.53 Gm. The erythrocyte count was 1,750,000. The leukocyte count was 48,100. There were a few normoblasts. There were 84 per cent neutrophils and 12 per cent lymphocytes. A stained smear showed numerous macrocytes and microspherocytes. The icteric index was 79. The patient's serum clumped her own cells and the cells of all four normal types. (Her father's serum also agglutinated cells of all normal types.)

The patient's temperature remained at 102 F., and the pulse rate ranged from 180 to 250 per minute. On February 14 the hemoglobin content was 5.0 Gm., the erythrocyte count was 1,100,000, the leukocyte count was 61,400 and the platelet count was 520,000 per cubic millimeter. The erythrocytes were not abnormally fragile to hypotonic salt solution; hemolysis began at 0.48 per cent and was complete at 0.38 per cent. The urine showed some albumin and many casts but no hemoglobin. The patient died. Permission for an autopsy was not obtained.

CASE 6.—D. H., a white man 67 years old, was seen in consultation on Dec. 31, 1941. He had been well until the age of 58 years, when he had a coronary occlusion followed by atrial fibrillation, which has persisted. About three years prior to examination glycosuria was noted and was thereafter easily controlled with insulin. In late September or early October 1941 he began to show pallor and tired easily. During November he felt fairly well, but his friends noticed that he was very pale. Early in December he was exhausted and noticed that his urine was dark. He had no pain. At that time the erythrocyte count was 3,200,000 per cubic millimeter. The hemoglobin content was 60 per cent.

On December 14 there was marked jaundice. The urine was dark but was not tested for bile. The pulse rate was 80 per minute. There were no petechiae. The spleen and the liver were not felt. There was no fever. The icteric index was 80. The erythrocyte count was 2,700,000 and the leukocyte count was 7,600. The hemoglobin content was 47 per cent. There were many poikilocytes and marked anisocytosis. There was marked basophilic stippling. No definite microspherocytes were seen. There were many [illegible]ocytes. The differential count was normal.

From December 17 to 31 he received five transfusions. His temperature rose gradually from 100 F. to 102 F. to 103 F. daily. There was no bile in the urine. The icteric index was 20. His Wassermann reaction was negative.

On December 31 he was extremely ill. The hemoglobin content was 28 per cent. The erythrocyte count was 1,500,000 and the leukocyte count was 6,300. There were 90 per cent neutrophils. The pulse rate was 140. His temperature was 103.6 F. The fragility of the erythrocytes to hypotonic salt solution was normal. His serum did not agglutinate or hemolyze his own or other erythrocytes of the same type as his. Nothing new was found by physical examination except that the tip of the spleen had become palpable. A blood culture was negative.

The diagnosis seemed clearly established except that the absence of spherocytes had not been noted in any previous case. Splenectomy was considered, but because of his age and the complicating diabetes mellitus and heart disease the operation seemed too hazardous. He was given numerous small transfusions. His jaundice slowly disappeared, and his blood became normal.

A few months later, however, pallor and jaundice reappeared, and the spleen again became palpable. The anemia became marked, and anisocytosis with macrocytosis and microcytosis was present. Only a few microspherocytes were ever present in stained films. The osmotic fragility of the erythrocytes was normal, and no autoagglutination was observed.

His condition became critical, and repeated transfusions only increased the icterus without influencing the anemia. The spleen was removed. Following this, the anemia improved, but secondary hyperthrombocytosis developed with multiple venous thromboses, from which he died.

Case 7.—A white woman 29 years old was admitted to the Los Angeles County Hospital on March 15, 1942. She complained that she had suffered from chills, fever, weakness, jaundice, headache and breathlessness for ten days. The illness began about two weeks before admission, when her color was said to be peculiar, and the whites of her eyes became yellow. Ten days before admission she was drenched by a cold rain, and that night she began to have chills and fever. She also had cough and a pounding headache. On March 18 she began to notice breathlessness. The jaundice became deeper, and nausea and vomiting developed.

She had had no serious illnesses previously. Her menstruation was normal. She had had four pregnancies. The first ended at six months, the second at six weeks. The last two resulted in normal births at term. A positive Wassermann reaction was present in 1939, and she received injections in the hips and veins. The last treatment was in November 1941. No other member of her family was known to have jaundice or anemia.

Her temperature was 102 F. The pulse rate was 120. The blood pressure was 130 systolic and 80 diastolic. There was marked icterus of the skin and of the scleras, and there was marked pallor. There were a few small hemorrhages in each fundus. There were no petechiae. The lymph nodes were not enlarged. The edge of the liver was about 6 cm. below the costal margin. The tip of the spleen was just felt.

The hemoglobin content was 22 per cent. The red cell count was 880,000 and the white count was 28,900 per cubic millimeter. There were 30 per cent reticulocytes. The differential count was normal. There were many macrocytes and normoblasts and many microspherocytes. The icteric index was 56. The urine contained a large amount of urobilin. The stool was very dark but contained no blood. With hypotonic saline solutions the red cells showed beginning hemolysis at 0.82 per cent and complete hemolysis at 0.28 per cent. There were no demonstrable autoantibodies or isoantibodies.

In the hospital the temperature remained between 101 and 104 F. The patient was given numeruos transfusions. Her blood picture and general condition improved. On April 19 her symptoms increased and her anemia began to increase.

On April 22 the hemoglobin content was 22 per cent, the red cell count was 1,100,000 and the white cell count was 8,700. The stained films of blood showed many macrocytes, microcytes and microspherocytes.

Her condition became worse rapidly, and on April 24 her spleen was removed. It was large, and sections showed some areas of necrosis. There was some phagocytosis. The pulp spaces were markedly congested.

No stones were present in the gallbladder. There were a number of enlarged lymph nodes, some as large as a walnut, along the greater curvature of the stomach.

On May 6 some fluid with inflammatory cellular content was removed from the left pleural cavity. Following this, the patient's condition improved.

On June 15 the hemoglobin content was 44 per cent, the red cell count was 2,370,000 and the white cell count was 14,400. There were numerous microspherocytes in the stained film. The icteric index was 13.

On July 13 the hemoglobin content was 69 per cent, the red cell count was 3,490,000 and the white cell count was 7,800. The stained smear showed marked anisocytosis with many macrocytes and microcytes and numerous microspherocytes. The fragility of the red cells to hypotonic saline solution was normal.

CASE 8.—J. S., a white man 44 years old, was admitted to the Los Angeles County Hospital on Oct. 13, 1941 and died on Nov. 3, 1941.

He complained of weakness, breathlessness on exertion, yellow skin and pallor of three months' duration. He stated that during the past five years he had had several episodes of jaundice and weakness with severe anemia. The first one followed a series of colds in the head. He was in a hospital at that time and was given injections of liver extract. Between the various attacks of jaundice he recovered and returned to work. The last attack before the present one was eighteen months ago.

About ten days before admission he had severe pain in the left upper quadrant of the abdomen, associated with pain on breathing.

Five years ago he had a number of attacks of pain in the right upper quadrant of the abdomen and was told he probably had gallstones. He never had clay-colored stools during any of these illnesses, although the urine was often quite dark. During the past three years his attacks of weakness, jaundice and anemia have not been associated with pain in the right upper quadrant.

His past history is otherwise irrelevant. So far as he knows, none of his family has had a similar illness.

The pulse rate was 78 per minute; the temperature was 102.4 F.; the blood pressure was 140 systolic and 50 diastolic. The patient seemed acutely ill. There was marked pallor, and the skin and the scleras were icteric. The tongue was not smooth. There was no abnormal enlargement of the lymph nodes. The lungs were normal. There was a loud systolic murmur over the body of the heart. The edge of the liver was felt about 6 cm. below the costal margin. The spleen was felt about 4 cm. below the costal margin. The liver was tender. The skin was normal except for the presence of a shallow ulcer, about 1 by 1.5 cm., on the lower part of the left leg.

On October 13 the erythrocyte count was 1,030,000, and the leukocyte count was 47,000 per cubic millimeter. The hemoglobin content was 22 per cent. There were many normoblasts. There was marked anisocytosis with many small, dark microspherocytes.

On October 14 the hemoglobin content was 4 Gm. (25 per cent), the erythrocyte count was 960,000, and the leukocyte count was 49,100 but was 22,300 when corrected for normoblasts. There were 23 per cent reticulocytes. There were 64.5 per cent neutrophils, 21 per cent lymphocytes, 11 per cent monocytes and 3.5 per cent other cells. There were 119,000 platelets per cubic millimeter. The smear showed anisocytosis with some macrocytes and numerous hyperchromic microspherocytes. The icteric index was 120. The urine contained large amounts of bile and urobilinogen. The patient's blood was type O (Moss group IV), but his serum agglutinated the cells of all donors and it also agglutinated his own red cells. Tests for fragility of his cells were set up; hemolysis began at 0.8 per cent and was not complete until 0.26 per cent hypotonic salt solution was reached.

On October 25 the patient was extremely ill. His temperature varied between 101 and 103 F. The nonprotein nitrogen amounted to 70 mg. per hundred cubic centimeters. The icteric index was 96. The serum albumin was 3.19 per cent and the serum globulin was 3.1 per cent. The prothrombin content was 60 per cent of normal. The hemoglobin content was 36 per cent. Cholecystotomy was done, and gallstones were removed. On October 29, following the removal of the gallstones, the patient's condition became critical, and splenectomy was performed. At that time his erythrocyte count was 900,000.

On October 31 the patient was gravely ill. His temperature was 103 F.; his pulse rate, 132 per minute. On November 1 the icteric index was 240. On November 3 the patient died.

After the spleen was removed, no further autoagglutination was noted during blood counts, and the resistance of the red cells returned to normal at the end of forty-eight hours.

Blood specimens from three sons of this patient were examined. The erythrocytes of none of them showed any increased fragility in saline solutions. The patient's brother's erythrocytes also showed no increase of fragility. The patient's Wassermann and Kahn reactions were negative.

Before each operation the following tests were made at room temperature:

	Patient's Serum	Group O Serum	No Serum
Patient's erythrocytes in 0.85 per cent sodium chloride solution	No hemolysis at 4 and 16 hr.	No hemolysis at 4 and 16 hr.	Moderate hemolysis
Patient's erythrocytes in 1.0 per cent sodium chloride solution	No hemolysis	No hemolysis	Slight hemolysis
Group O erythrocytes in 0.85 per cent sodium chloride solution	No hemolysis	No hemolysis	No hemolysis

The patient's serum agglutinated his own red cells and red cells of all normal types, but no hemolysins could be demonstrated. The spleen weighed 600 Gm. and was purplish red.

The pulp spaces were packed with red cells, and the splenic sinuses were obliterated. There was some hemosiderosis, and a few macrophages contained erythrocytes. No other lesion of importance was found at autopsy.

CASE 9.—A. C., a white girl 17 years old, was admitted to the Hospital of the Good Samaritan, in Los Angeles, on Dec. 8, 1939 and was discharged on Jan. 29, 1940.

At the age of 7 years she began to have attacks of severe pain in the upper abdominal region. At that time the spleen was enlarged. With the attacks she had nausea and vomiting. Often several months intervened between the attacks of pain. During these years she was often quite anemic, and her mother thought there was some relation between the attacks and the anemia. At one time the hemoglobin content was as low as 36 per cent. She had some fever with each of the attacks. She was given three transfusions during those years. She never had abnormal bleeding of any type. About three weeks before the present admission she had a severe attack of pain in the upper part of the abdomen, and in a few days her skin was quite yellow. She had a high fever and was very ill.

The tonsils had been removed. She had had measles, mumps and pertussis. Her menstrual history was normal. There were no siblings, and the family history revealed no similar disease, although her mother had had gallstones removed.

Physical examination showed a patient strikingly pale and deeply icteric. She was acutely ill and moderately delirious. Her temperature was 100 F. The blood pressure was 100 systolic and 70 diastolic. There were no petechiae. The lymph nodes were not enlarged. The liver was not enlarged. The soft edge of the spleen was felt just above the umbilicus.

On December 8 she had a convulsion, and on December 9 she had three more convulsions. The jaundice was marked. The urine contained bile and a heavy trace of albumin. The hemoglobin content was 66 per cent. The erythrocyte count was 4,000,000. The leukocyte count was 11,000. There were 87.5 per cent neutrophils. The icteric index was 700. The sedimentation rate was 12 mm. in twenty-four minutes (normal, 120 minutes). The blood cholesterol amounted to 284 mg. per hundred cubic centimeters. The Wassermann reaction was normal.

On December 11 the patient was intensely icteric. There was no bile in the stool. A roentgenogram of the abdomen showed a large spleen, a slightly enlarged liver, ten gallstones in the gallbladder and one in the region of the ampulla. Roentgenograms of the bones showed no changes of congenital hemolytic icterus. On December 15 the hemoglobin content was 30 per cent. The leukocyte count was 4,100 and the erythrocyte count 2,000,000. One normoblast was seen. Many spherocytes were present. The coagulation time was fifty-five minutes (Howell method). The icteric index was 160.

On December 18 the fragility of the erythrocytes to hypotonic saline solution was normal No autohemolysins or autoagglutinins were demonstrated.

On December 21 cholecystotomy was performed. Ten stones were removed, and the common duct was probed. The icteric index was 74.

On December 26 the hemoglobin content was 67 per cent. On January 27 the icteric index was 30.

Course of the Disease.—From December 9 to December 15 the hemoglobin content decreased from 66 to 30 per cent. During that time there was extreme hemolysis and, in addition, the stools were acholic from obstruction of the common duct.

During the first week in the hospital her fever was low, but from December 14 to January 10, 1940 she was delirious or comatose and her temperature varied from 102 to 104 F. Following this period, the hemolysis became less, the hemoglobin increased and the temperature returned to normal.

This patient has been observed on many occasions since the early part of 1940. On all occasions she was anemic and icteric, and the spleen was felt near the level of the umbilicus. The latest blood count at the time of writing was made in Frebuary 1942. The hemoglobin content was 52 per cent. The red cell count was 4,300,000, and the white cell count was 7,900 with 65 per cent neutrophils. There were large numbers of microspherocytes and a few macrocytes. The reticulocytes were 16 per cent.

CASE 10.—H. I., a Japanese girl 15 years of age, was first seen in October 1938. About two weeks previously she began to have jaundice. By December 27 the jaundice was deeper, and she was admitted to the hospital.

She had been well previously, although she had lost 10 pounds (4.5 Kg.) in the past three months. Neither parent had had jaundice.

On admission her temperature was 99.4 F. The tonsils were large. The spleen and the liver were not felt. The hemoglobin content was 37 per cent. The red cell count was 1,380,000. The white cell count was 10,400. The color index was 1.4. The differential count was normal. There were many macrocytes and microcytes and numerous normoblasts. The

reticulocyte percentage was 84. The icteric index was 40. Hemolysis in hypotonic saline solutions began at 0.50 per cent and was complete at 0.40 per cent. The diameter of the red cells varied from 4 to 11 microns.

On Jan. 27, 1939 the spleen was removed because the patient was believed to have congenital hemolytic jaundice.

On March 27 the hemoglobin content was 77 per cent, and the white cell count was 8,600. The patient felt well, but she was still icteric.

On August 10 the icteric index was 260, the hemoglobin content was 41 per cent, and the white cell count was 15,150. There were numerous microcytes and normoblasts.

On Jan. 2, 1940 she was admitted to the Los Angeles County Hospital. She complained of weakness, nausea, vomiting and jaundice. She was found to have deep jaundice. Her temperature was 103 F. The edge of the liver was 5 cm. below the costal margin. The red cell count was 980,000. The white cell count was 70,000 (uncorrected for normoblasts). Fragility tests with hypotonic saline solutions showed hemolysis beginning at 0.72 per cent and complete at 0.42 per cent.

Her temperature rose to 102 F. or more each day. On January 14 the icteric index was 364.

On January 5 the hemoglobin content was 44 per cent, the red cell count was 1,660,000 and the white cell count was 82,150 (when corrected for normoblasts it was 16,680). The differential count was normal. With hypotonic saline solutions, hemolysis began at 0.72 per cent and was complete at 0.26 per cent. There were numerous macrocytes, normoblasts and spherocytes at all times, and the reticulocytes were greatly increased.

On January 22 tests for fragility of erythrocytes showed initial hemolysis at 0.84 per cent and complete hemolysis at 0.34 per cent. Approximately the same results were obtained ten days later. The patient continued to have fever daily. She was given three transfusions. On March 1 the red cell count was 2,500,000, the white cell count was 20,600 and the hemoglobin content was 70 per cent. The smear showed many macrocytes, normoblasts and spherocytes. The icteric index was 44. The urine contained bile and a large amount of urobilinogen.

On March 27 the patient had improved slowly. Her fever had nearly disappeared. The abdomen was searched for an accessory spleen or hemolymph nodes. None was found. The gallbladder was removed, and it was essentially normal but contained ten small soft pigment stones.

On June 14 the patient was icteric. The icteric index was 20. The hemoglobin content was 64 per cent. The red cell count was 2,820,000 and the white cell count was 9,550. The color index was 1.26. The reticulocyte percentage was 20.4. Five normoblasts were seen. The smear showed many macrocytes and numerous spherocytes.

Tests for autoagglutination and isoagglutination were not made at any time. However, since typing for transfusion was not difficult, one may assume that there was no isoantibody present.

Case 11.—F. F., a white woman 55 years old, was admitted to the Los Angeles County Hospital on Sept. 7, 1941. She complained of jaundice of eight months' duration.

Three years previously her gallbladder was removed, but no stones were found. Four months later the abdomen was again explored. Since then she had felt weak and run down.

Eight months before admission she became ill with fever, chills and jaundice, and these had been present at intervals up to the time of admission. She had vomited frequently and had had some abdominal pain during the past eight months. During that time she had seven blood transfusions to relieve her anemia.

Her father died of pneumonia, and her mother died of renal trouble. She had six siblings living and well. None had jaundice. She had two children, aged 33 and 36, living and well.

Her appendix was removed at the age of 25 years. Afterward an ovarian cyst and the tonsils were removed, and a ventral hernia was repaired. She had a normal menopause at 41 years of age.

On physical examination her temperature was 102.2 F. The blood pressure was 130 systolic and 80 diastolic. She appeared chronically ill. She was pale and jaundiced. There were no petechiae, angiomas or enlarged lymph nodes. The heart and the lungs were normal. The edge of the liver was felt about 5 cm. below the costal margin. The lower border of the spleen was palpable 8 cm. below the costal margin.

On September 9 the hemoglobin content was 44 per cent, the red cell count was 2,360,000 and the white cell count was 14,100. There were 84 per cent neutrophils and 16 per cent mononuclear cells. The urine was loaded with pus and Escherichia coli. Her temperature was 104 F. Several stools were examined, and no abnormalities were noted. The icteric index was 28. The blood cholesterol amounted to 165 mg. per hundred cubic centimeters. The prothrombin content was 75 per cent of normal. The bleeding time was one minute; the

clotting time was six minutes; the clot retraction was normal. Tests for fragility of red cells showed initial hemolysis at 0.56 per cent and complete hemolysis at 0.26 per cent.

On September 17 the hemoglobin content was 8.5 Gm., and the red cell count was 2,590,000. The hematocrit reading was 22 cc. of packed cells per hundred cubic centimeters of blood. The volume index was 1.04. The mean cell volume was 88 cubic microns and the mean cell hemoglobin content was 34 micromicrograms. There were many macrocytes and spherocytes. The bone marrow was said to be consistent with the diagnosis of congenital hemolytic jaundice. Several blood cultures were negative. On October 21 the fragility test showed beginning hemolysis at 0.6 per cent and complete at 0.26 per cent. The Wassermann reaction was negative. The urine contained an excess of urobilinogen.

The patient's condition became steadily worse, and she was believed to have an obstruction of the bowel. On September 22 the abdomen was opened. There were many adhesions. Nothing of importance was visualized, and nothing was done. The postoperative course was stormy, but she recovered. Some ascites was present for several weeks and then disappeared.

On October 28 the hemoglobin content was 60 per cent, and the red cell count was 2,110,000. She had continuous pyuria and apparently pyelonephritis.

On March 8, 1942, the hemoglobin content was 50 per cent, the red cell count was 2,010,000 and the white cell count was 7,100. A differential count was normal. There were 10 per cent reticulocytes. The fragility test with hypotonic saline solutions showed initial hemolysis at 0.72 per cent and complete hemolysis at 0.26 per cent. The stained smear showed many macrocytes and microspherocytes. The icteric index was 13.

The patient went home but was readmitted to the hospital May 14. She complained of burning and frequency of urination. Her legs were slightly swollen. There was considerable pain in the left upper quadrant of the abdomen. Her blood pressure was 154 systolic and 92 diastolic. The spleen reached to the umbilicus. The liver was just felt. There was a blowing systolic murmur at the apex, but the heart was otherwise normal. There was slight jaundice.

The urine contained numerous pus cells, but no albumin or casts were found.

On May 15 the nonprotein nitrogen amounted to 40 mg. per hundred cubic centimeters. The serum albumin was 4 per cent, and the serum globulin was 2.5 per cent. The icteric index was 25. An electrocardiogram was normal. The hemoglobin content was 51 per cent. The red cell count was 2,100,000. The white cell count was 8,400. The reticulocyte count was 23 per cent. The differential count was normal. The smear showed many macrocytes and microcytes and numerous microspherocytes. With hypotonic saline solution, hemolysis of the red cells began at 0.68 per cent and was complete at 0.28 per cent.

On June 8 the icteric index was 51. The urine was essentially normal, and it was believed that the pyelitis was cured.

On June 13 the spleen was removed. It weighed 680 Gm. Sections showed only marked congestion of the pulp spaces with obliteration of the sinuses. A few macrophages containing erythrocytes were seen.

On June 15 the hemoglobin content was 78 per cent, the red cell count was 3,560,000 and the white cell count was 11,800. A stained film showed numerous macrocytes and microcytes.

The patient continued to improve, but blood smears studied in August 1942 still showed the characteristic changes of the red blood cells. Thus the symptoms had been relieved, but the evidences of the disease in the altered appearance of the red cells still persisted.

Case 12.—H. S., a white woman 64 years old, was admitted to the Hospital of the Good Samaritan, in Los Angeles, on June 4, 1942. She complained of weakness, breathlessness and irregular beating of the heart.

She first noticed her illness about two years previously, when she began to have increasing weakness and nervousness. In January 1942 she became very weak and short of breath, and she noticed that her skin was pale. Numbness of the hands developed, and her gait was uncertain. She was given iron and injections of liver daily, but she did not improve.

During the two months prior to her admission to the hospital she had been given four transfusions without relief. About a month before, she noticed that her skin was yellow.

Physical examination showed nothing remarkable except pallor, moderate jaundice and a large spleen with the edge reaching to the level of the umbilicus. The spleen was not tender. There were no petechiae, no swelling of the gums and no enlarged lymph nodes. The deep and superficial reflexes were all normal. The sense of position and vibratory sense were normal.

The urine had a specific gravity of 1.017 and contained no sugar; a faint trace of albumin was present. Urobilinogen was positive in the dilution 1:130.

The hemoglobin content was 31 per cent. The red cell count was 1,600,000. The leukocyte count was 5,000, with a normal distribution of the cell types. There were moderate numbers of macrocytes and spherocytes. There were 24.4 per cent reticulocytes. The icteric index was 32. The hematocrit reading of the packed cell volume in a Sahli tube was 16 per cent.

The Wassermann reaction was negative. The patient's blood belonged to type IV (O). The van den Bergh test gave a negative direct reaction. With hypotonic saline solution, hemolysis began at 0.4 per cent and was complete at 0.3 per cent. In hanging drop preparations the patient's serum agglutinated her own red cells. No evidence of autohemolysis was present.

The patient had a low grade fever, with a temperature between 99 and 100 F.

On June 5, 1942 the hematocrit reading was 16 per cent with the Sahli tube. The reticulocyte count was 24.4 per cent, and the icteric index was 32.

On June 17 the spleen was removed by Dr. C. F. Sturgeon. It weighed 1,950 Gm. and measured 35 by 20 by 12 cm. It was soft and contained innumerable tiny gray areas, which were probably hyperplastic lymph follicles. Sections showed numerous malpighian bodies. The spleen was very cellular, and the pulp spaces were distended with blood.

On June 18 the hemoglobin content was 48 per cent.

On July 8 the hemoglobin content was 73 per cent, and the red cell count was 4,000,000. The stained film showed slight anisocytosis, but no microspherocytes were present. The icteric index was 9. The patient seemed entirely well, and her blood had returned to normal. At operation her gallbladder contained a few stones, but these were not removed.

RÉSUMÉ OF OBSERVATIONS

The clinical features of the acute form of acquired hemolytic anemia have been very similar in all of the reported cases. In children the disease usually has had an abrupt onset with chills and fever and frequently has run its course in a week or ten days, or even less. In adults there was as a rule a period of variable duration marked by increasing fatigue, weakness and malaise. In a few cases this period was brief but most of our patients when questioned carefully recalled that their symptoms began insidiously a few weeks or even a few months before they consulted a physician. By that time the usual complaints were exhaustion, dizziness, anorexia, nausea, vomiting and often abdominal cramps. Some patients also complained of headache, breathlessness and faintness on exertion.

On the first examination pallor and jaundice were always present, and there was some fever. Following this period, the symptoms frequently became more severe rapidly. The temperature usually varied between 101 and 104 F. but was occasionally higher. Chills were frequently present. The anemia usually became profound. Jaundice increased, and the patient at times became delirious or even had convulsions. At this later period physical examination as a rule showed only jaundice, pallor and slight enlargement of the spleen and possibly of the liver. One patient presented a remarkable erythematous lesion of the skin. The stools were often dark owing to the presence of large quantities of bile pigment, and the urine also contained large amounts of bile and urobilinogen. In some patients, after a variable number of transfusions, the symptoms ameliorated and complete recovery took place. This result in the reported cases seemed to be especially frequent in children. In other patients transfusions produced intensification of the icterus and fever without any gain in hemoglobin, while in still other patients severe reactions to transfusion occurred. In some instances the patient's condition soon became critical, and splenectomy had to be performed as a life-saving measure.

The duration of the acute type of acquired hemolytic anemia has varied considerably. There was a fulminating type, especially in children, which ran its course in a few weeks or less, and there was a subacute type lasting from a month to three months or more. Since any separation into acute and subacute types is purely arbitrary, I have grouped these cases together as examples of acute acquired hemolytic anemia of unknown cause. In addition to this group I have observed a number of cases of a chronic type marked by acute hemolytic crises, often of extreme severity, and by marked instability of the hemolytic balance of the red cells but otherwise presenting the same hematologic features as the

acute type, although somewhat modified in intensity. Moreover, as I shall mention later, I am of the opinion that the chronic is really more frequent than the acute type, although the latter has been reported more frequently.

The hematologic features of acute hemolytic anemia are of considerable interest. There is usually a leukocyte count greater than 15,000 per cubic millimeter (after making allowance for nucleated red cells) with a normal distribution of the cell types and a marked shift to the left. The erythrocyte count frequently drops to a million or below, and the color index is either at unity or usually slightly higher. The stained smear shows numerous macrocytes, containing normal or slightly less than normal quantities of hemoglobin. In addition there are numerous, deeply staining microspherocytes. Nucleated red cells are frequent and may be abundant. There are some, but not a large number of, poikilocytes. Many red cells show diffuse and punctate basophilia. The number of reticulocytes is always increased and may be as large as 80 per cent or more. The platelet count is normal.

The blood picture is characteristic and when typical is practically pathognomonic of the disease. It is, of course, dependent on rapid destruction of blood, probably of large numbers of spherocytes, and, pari passu, rapid regenerations of blood with reflection in the blood stream of all the types of cells of a hyperplastic, regenerative bone marrow of normoblastic type.

The rapidity of the destruction of blood in the hemolytic crisis is great. In many patients the red cell count may drop a million a day and the loss of hemoglobin may be nearly as large proportionately. Even with this enormous destruction of red cells, the stained smears of the blood show all the features of intense regenerative activity of the bone marrow. No evidence of exhaustion, injury or dysfunction of the marrow has been present in patients with the acute or the chronic type of the disease. In 2 patients who died during the acute hemolytic crisis there was also no morphologic evidence of terminal exhaustion of the marrow. In a number of patients with the chronic form of acquired hemolytic icterus death was due to the profound anemia combined with hepatic insufficiency as the result of hepatic fibrosis produced by intrahepatic and extrahepatic pigment stones in the biliary system and the resultant chronic infection in the biliary ducts.

Thus the characteristic blood picture of acquired hemolytic anemia consists of profound anemia with numerous macrocytes and spherocytes, a color index at or above unity, marked reticulocytosis with other evidences of immaturity of the macrocytes, numerous normoblasts and leukocytosis. This type of morphologic alteration of the red cells was called pseudomacrocytosis by Dameshek and Schwartz, and this term aptly describes the changes in the red blood cells.

An infrequent hematologic phenomenon in acute hemolytic anemia has been the presence of an autoagglutinin or of an isoagglutinin and in some cases of an isohemolysin and/or an autohemolysin. I was not able to demonstrate autohemolysis or isohemolysis in any of my patients. An autoagglutinin and/or an isoagglutinin, however, was present in 4 patients (cases 2, 5, 8 and 12). The serum of the healthy father of one of these patients also contained an isoagglutinin for all normal types of red cells. One of these patients, early in the disease, had an autoagglutinin and an isoaggultinin for all except type O cells. Later her serum agglutinated her father's cells, which were type O. Another patient had an autoagglutinin and an isoagglutinin for all normal types of erythrocytes, but these antibodies disappeared a few hours after the spleen was removed.

The resistance of the red cells to hypotonic solutions of sodium chloride has been normal in the majority of the reported cases. In a number of instances the

fragility of the red cells has been greatly increased. Since spherocytes were present in the blood in all of my patients with this disease, although in very small numbers in 1 patient, it is not their presence alone which determines the increased fragility. Neither is the diminished resistance of the red cells dependent on the presence of autoantibodies or isoantibodies, since these antibodies are frequently not present in the serum of patients with the disease. The fragility of the red cells of most of my patients was normal. With hypotonic saline solutions the hemolysis of the red cells of 1 patient began at 0.85 per cent and was complete at 0.26 per cent. The red cells of another showed beginning hemolysis at 0.82 per cent and complete hemolysis at 0.28 per cent. The red cells of a third patient showed beginning hemolysis at 0.8 per cent and complete hemolysis at 0.26 per cent. With those of a fourth patient hemolysis began at 0.84 per cent and was complete at 0.34 per cent. This unusually wide difference in hypotonicity between beginning and complete hemolysis is seldom seen in any other disease so far as I know. Its significance will be discussed later.

Hemoglobinuria was not present in any of my patients or in the patients observed by Dameshek and Schwartz.[15] In regard to the more fulminating type of the disease in children, Atkinson[16] found that hemoglobinuria has been reported in about 30 per cent of the cases. The rarity of the presence of hemoglobinuria is probably of considerable importance in the genesis of the malady and will be discussed later.

The pathologic changes have usually been described as follows: moderate enlargement of the spleen, with packing of the splenic pulp with red cells to such a degree that the normal venous sinuses have been obliterated; presence of hyaline thrombi in the radicles of the splenic vein or in the small peripheral venules; marked hyperplasia of the bone marrow; hemosiderosis of the spleen and liver and some degree of erythrophagocytosis[17] in both of these organs, and usually marked hyperplasia of reticuloendothelial cells in the spleen, the liver and the bone-marrow.

The marrow of 3 patients studied by Dameshek and Schwartz[15]

> . . . showed in each instance a very hyperplastic marrow with marked predominance of erythroblastic cells. Many of the early nucleated red cells . . . resembled megaloblasts, but careful examination demonstrated that the resemblance was only superficial. In any event, the most mature nucleated red cells . . . were definitely normoblastic and showed none of the megaloblastic criteria. The marrow was thus "normoblastic" and could readily be differentiated from the typically megaloblastic marrow of the liver-extract deficiency state (pernicious anemia).

COMMENT

I have described briefly the chief clinical and hematologic features of acquired hemolytic anemia, and an attempt will be made to correlate these with the theoretic and experimental observations which may have some importance in any consideration of the genesis of the malady.

The most striking feature of the stained blood film of the patient with the disease is the presence of large numbers of macrocytes and spherocytes. In general, from a study of the smear one gets the impression that the average

16. Atkinson, F. R. B.: Lederer's Anemia, Brit. J. Child. Dis. **37**:35, 1940.

17. Recently Hargraves, Herrell and Pearman[18] reported a case of erythrophagocytosis of high degree in the peripheral blood, involving monocytes, macrophages and leukocytes. The patient recovered following transfusion of blood. The clinical features resembled those of acute hemolytic anemia (acquired type), and the case was reported under the title "Erythrophagocytic Anemia (Lederer's Anemia?)." However, peripheral erythrophagocytosis has not been reported in Lederer's anemia nor in acquired hemolytic anemia.

diameter of the red cells is greater than normal in spite of the presence of numerous small deeply stained spherocytes. In addition the color index is usually at unity or even above.

The peripheral blood always shows evidences of increased regenerative demands on the bone marrow. In addition to the macrocytes there may be as many as 80 per cent reticulocytes and large numbers of normoblasts during the period of active hemolysis. Both autopsy and biopsy specimens of bone marrow have shown a hyperplastic, normoblastic marrow without other significant abnormalities. The presence of large numbers of spherocytes in the blood in this disease is of great diagnostic importance, although its significance is not yet entirely clear in spite of many dogmatic statements concerning the origin of these cells.[18] Haden [19] in a recent review of his own observations and of those of previous investigators accepted the common belief that the spherocyte is a red cell which has been injured by one of various means. According to this theory, one may assume that the life span of the spherocyte has been shortened by such an injury and that it will soon be destroyed by some means somewhere in the body. He stated that in congenital hemolytic icterus these cells are probably abnormally formed in the bone marrow although in certain other maladies they may acquire their spheroidal shape after leaving the marrow. Dameshek and Schwartz [18] concluded that spherocytes are formed outside of the marrow and that they represent mature red cells which have been damaged by various types of hemolytic agents. This is the prevailing belief at the present time, and most observers agree that the spherocyte is a cell of lowered resistance that was damaged after its birth and was not therefore originally an abnormally formed cell. I believe, furthermore, that the spherocyte is not necessarily of lowered osmotic resistance, although its resistance to other hemolytic agents may be diminished.

In congenital hemolytic icterus spherocytosis and increased fragility in hypotonic solutions of sodium chloride are constantly present. Neither one of these abnormalities completely disappears, although both may diminish, after splenectomy, a procedure which abolishes all other manifestations of the disease. In acute acquired hemolytic anemia spherocytosis is also constantly present, although increased fragility of the red cells in hypotonic saline solutions is only occasionally observed. Apparently in the latter disease the diminished resistance of the red cells to hypotonic solutions does not parallel the extent of the damage to the red cells by the hemolytic agent, the number of spherocytes in the circulating blood, the degree of anemia or the presence of autoantibodies in the serum. At the moment, therefore, it is not possible to explain the variable behavior of the spherocytes of acquired hemolytic anemia with hypotonic saline solutions. Both the spherocytosis and the increased fragility may be quickly abolished by splenectomy in some cases or apparently cured by transfusions of blood in other cases. In the hemolytic anemia reported as Lederer's anemia a single, small transfusion has been followed occasionally by complete cure. I was not able to find spherocytes in the blood of a patient with severe paroxysmal nocturnal hemoglobinuria (Marchiafava-Micheli syndrome), nor were Buell and Mettier.[20] Neither has their

18. Hargraves, M. M.; Herrell, W. E., and Pearman, P. O.: Erythrophagocytic Anemia (Lederer's Anemia?): Report of a Case with Recovery, Proc. Staff Meet., Mayo Clin. **16**:107, 1941.

19. Haden, R. L.: The Nature of Hemolytic Anemia, in A Symposium on the Blood and Blood-Forming Organs, Madison, University of Wisconsin Press, 1939, p. 83.

20. Buell, A., and Mettier, S. R.: Paroxysmal Nocturnal Hemoglobinuria with Hemolytic Anemia (Marchiafava-Micheli Syndrome), J. Lab. & Clin. Med. **26**:1434, 1941.

presence been reported in cold-hemoglobinuria nor in march-hemoglobinuria.[21] Dameshek and Schwartz[15] were able to produce spherocytes by the injection of hemolytic serum or certain hemolytic agents into the blood stream. Ham and Castle[22] showed that when erythrostasis was imitated in vitro by sterile incubation of defibrinated human blood the cells increased in volume, in spheroidicity and in osmotic fragility. Others had previously shown that in bloody spinal fluid and in hemothorax a hemolysin was produced and that the red cells gradually showed increased fragility and increased spherodidicity before disintegration occurred. Thus it is probable that the striking congestion of the spleen in acquired hemolytic anemia is in some way dependent on the alteration of the physical behavior of the red cells produced by the action of some hemolysin which damages them in the blood stream. Since these damaged red cells are probably unable to leave the spleen, for reasons not now known, erythrostasis in that organ becomes increasingly intense and this produces further alterations of these injured red cells, with increase of the rate of their dissolution by the normal action of the spleen and of the reticuloendothelial system.

In acquired hemolytic anemia, therefore, it is probable that some hemolytic agent acting on the red cells in the peripheral circulation increases their spheroidicity and in some instances also increases their fragility as tested with hypotonic saline solutions. Since these injured cells are not destroyed at once in the blood stream, they eventually enter the spleen, where they are held back for destruction. Thus the spleen becomes engorged in nearly all types of hemolytic anemia. Erythrostasis in the spleen increases as the disease progresses, and it is probable that this factor may play an important part in the increasing tempo of hemolysis in the acute phase of the acute hemolytic crisis. Thus the red cell which has been injured but not destroyed in the peripheral vessel succumbs more or less rapidly to the normal destructive action of the spleen on effete red cells augmented by the deleterious influence of erythrostasis in the spleen on the erythrocytes. In certain fulminating types of acute acquired hemolytic anemia hyaline thrombi have been extensive in the terminal vessels. Since they are produced by the conglutination of red cells, it is further evidence of the effect of stasis on the injured red cells in the more severe types of this disease no matter whether the stasis occurs in the spleen or in the peripheral arterioles.

This conception of the role of the spleen in the genesis of the disease seems to correlate with the facts known at the present time. However, since the cause of acquired hemolytic anemia obviously does not reside in the spleen removal of this organ will not cure the disease in every instance. In some cases the damage to the red cells by the hemolytic agent may be so great that even removing the destructive influence of the spleen and of erythrostasis in the spleen may not be sufficient to carry the patient through the acute phase of the disease or to tide him over the critical period before the hemolytic agent either leaves the blood stream spontaneously or becomes less active in those instances in which the disease is doomed to run a chronic course.

There is another feature of acute hemolytic anemia which may be of fundamental importance in any theory of the genesis of the disease. In my cases and in those reported by Dameshek and Schwartz,[15] in spite of the extreme rapidity of the hemolysis, no discoloration of the urine by hemoglobin was observed. In all of the patients the icterus was of high degree. In the various types of hemoglobinuria,

21. Gilligan, D. R., and Blumgart, H. L.: March Hemoglobinuria, Medicine **20**:341, 1941.

22. Ham, H. H., and Castle, W. B.: Relation of Increased Hypotonic Fragility and of Erythrostasis to the Mechanism of Hemolysis in Certain Anemias, Tr. A. Am. Physicians **55**:127, 1940.

on the contrary, the hemoglobinuria and the hemoglobinemia may be marked although spherocytes are absent, icterus is mild and the degree of anemia is slight in comparison with the marked hemoglobinuria.

The frequency of hemoglobinuria in patients with acquired hemolytic anemia is not known accurately, although Atkinson [16] reported that it was present in 11 of 30 children with all types of acute hemolytic anemia. In this connection Dameshek and Schwartz [15] stated that when an immune hemolysin is injected into the blood stream of guinea pigs in different doses, various results are obtained. With large doses there is a fulminating anemia with hemoglobinuria, while with small doses there is a "pseudomacrocytic" anemia without hemoglobinuria. I have obtained these results by injecting rabbit serum immune to human red cells into patients with multiple sclerosis. However, I believe these experimental results oversimplify the problem. It is probable that in acquired hemolytic anemia the hemolytic agent acting on the blood cells, probably in some portion of the peripheral blood stream, is either small in amount or of low potency and that the red blood cells injured by it are consequently destroyed only in the spleen and are not hemolyzed in the general vascular system. In hemoglobinuria, on the contrary, the hemolytic agent is of small amount but of high potency, and the cells injured by it are hemolyzed largely in the blood stream before they reach the spleen and their hemoglobin is therefore set free in the blood vessels. Since the renal threshold for hemoglobin in man is about 135 mg. of hemoglobin per hundred cubic centimeters of blood,[23] it is apparent that only small quantities of hemoglobin need to be liberated into the blood vessels to cause marked hemoglobinuria. In acquired hemolytic anemia, on the contrary, the red cells injured in the blood stream by the hemolytic agent of the disease are destroyed only in the spleen, and free hemoglobin does not enter the blood stream unless the amount of hemoglobin liberated by the hemolysis overwhelms the spleen and the liver. In hemoglobinuria the hemolytic agent destroys the red cells and liberates the hemoglobin in the blood stream, and most of it leaves the body through the kidney just as if hemoglobin had been injected into the blood vessels. In support of this hypothesis Gilligan and Blumgart [21] in a study of march hemoglobinuria found that even though the hemoglobinuria was of marked degree no appreciable anemia was observed in their patients, and the same general results have been observed frequently in cold-hemoglobinuria and in paroxysmal nocturnal hemoglobinuria.

One of the more interesting features of acquired hemolytic anemia occasionally reported is the presence of agglutinins or of hemolysins in the serum. Widal, Abrami and Brulé [5] and Chauffard and Troisier [6] observed the phenomena associated with these and were convinced of their importance in the genesis of the disease. They assumed that the hemolysins might be endogenous or exogenous in origin. Widal and Abrami [8] expressed the belief that the red cells in acute acquired hemolytic anemia were changed to spherocytes in the blood stream by the action of a hemolytic substance. They assumed that the malady could be explained by the theory of hemolysis developed by Bordet.

The hemolysins, according to this hypothesis, are practically completely absorbed by their specific antigen, the red cell. This combination of hemolysin and antigen will then absorb most of the complement. Thus in vitro the serum will be nonhemolytic, since all the hemolysin is absorbed by its antigen. The content of complement will be diminished or even absent, since it is in great part attached to the antigen-antibody union. The red cells will be completely hemolyzed if the amounts of hemolysin and complement are sufficient. If these quantities are

23. Yuile, C. L.: Hemoglobinuria, Physiol. Rev. **22**:19, 1942.

incomplete, the red cells will be fragile and will be hemolyzed only after the addition of more complement. In the patient with acute hemolytic anemia "the red cells are fragile to hypotonic saline solution, just as sensitized red cells are after they have been given a small dose of complement, and they will dissolve completely when placed in serum rich in complement, just as red cells sensitized to a hemolysin would." The serum in vitro has no hemolytic action since all the hemolysin is fixed by the red cells. Thus the serum acts as though it contained an anticomplementary substance, and it is probable that it is the unstable equilibrium acting without ceasing between the circulating hemolysin and the antihemolysin which causes the incessant variations of the state of the blood in this malady. Chauffard and Troisier [6] first found a hemolysin in the serum of a patient with acquired hemolytic anemia. This serum contained an autohemolysin and also an isohemolysin which disappeared when it was heated to 56 C. but which returned when complement was added. They believed that the autoantibody was of fundamental importance in the disease, and they assumed, therefore, that acquired hemolytic anemia was really a hemolysinic anemia and so named the disease.

The problems concerning the relation of the autoantibodies and isoantibodies to the genesis of the disease were discussed in a recent article by Reisner and Kalkstein.[24] According to these authors, Wiener in a personal communication expressed his opinion that the autoantibodies were a symptom and a result of the disease rather than its cause. Apparently he expressed the belief that when massive destruction of red cells occurs, the destroyed red cells themselves under certain conditions may stimulate formation of autoantibodies. "When only a small amount of hemolysis occurs the reticulo-endothelial system can take care of the effete cells, but when large amounts of blood are destroyed the accessory mechanisms of autoantibody formation are brought into play." They stated that agglutination and hemolysis of red cells are due to the identical immune antibody acting under different conditions. "Therefore, we believe that although they may not always be found without special examination, autoagglutinins are likely to occur in most cases of autohemolytic anemia, and conversely the presence of autoagglutination in such cases may be so marked as to interfere with the satisfactory in vitro demonstration of auto-hemolysins." They also searched the literature and found reports of 54 instances of autoagglutination in various diseases. In many of these and in a number which I have observed no evidence of hemolysis or of hemolytic anemia was present clinically.

I was not able to demonstrate the presence of hemolysins in the serum of any of my patients. One patient (case 2) had an autoagglutinin to her own cells, type AB, and to all AB cells. Early in the disease her serum did not agglutinate her father's cells, which were type O, but later it did. The serum of another patient (case 5) agglutinated her own cells and the cells of all other normal types. Her father's serum also agglutinated all normal cell types but was not tested against his own cells. He was well and healthy and I have no explanation for the presence of an isoagglutinin in his blood. The serum of the third patient (case 8) agglutinated his own cells and all other normal type red cells, but I was unable to demonstrate any hemolysins. It is remarkable that in this instance the agglutinin disappeared in less than forty-eight hours after splenectomy. Autoagglutinins were also present in a fourth patient (case 12) of my series.

There is no convincing evidence at the present time that these antibodies are true immunologic antibodies nor are they normal human agglutinins since they

24. Reisner, E. H., Jr., and Kalkstein, M.: Autohemolysinic Anemia with Auto-Agglutination: Improvement After Splenectomy, Am. J. M. Sc. **203**:313, 1942.

frequently agglutinate type O cells. They are not demonstrable in every case of acquired hemolytic anemia, and they may be present in the serum of healthy persons and in the serum of patients with a variety of diseases unassociated with any type of hemolytic anemia. One cannot dismiss them as of no importance in the genesis of acquired hemolytic anemia, yet their irregular appearance in the malady and their rapid disappearance after splenectomy in at least 1 of my patients lead me to favor the belief that their presence may be in some way determined by destruction of blood and erythrostasis in the spleen and that these antibodies are, therefore, not the causal factor in the disease nor the essential factor in the production of hemolysis. Theoretic considerations unsupported by sufficient facts are not warranted at present, and one may hope that in the future this problem may be studied more carefully as the disease is recognized more frequently.

The fragility of the red cells as tested with hypotonic saline solutions has been increased in a number of cases of acute acquired hemolytic anemia, although in the majority of instances it was normal. In 3 of my cases and in the case observed by Moschcowitz [11] the type of diminished resistance of the red cells was different from that I have seen in any other disease. In 1 of my cases hemolysis began at 0.85 per cent and was complete at 0.26 per cent. In another hemolysis began at 0.82 per cent and was complete at 0.28 per cent. In a third hemolysis began at 0.8 per cent and was complete at 0.26 per cent. In Moschcowitz' case hemolysis began at 0.8 per cent and was complete at 0.19 per cent.

In order to explain, if possible, the wide difference in hypotonicity between beginning and complete hemolysis one might assume that the young red cells are more resistant than normal and that the spherocytes are more fragile than normal cells. I checked the sediment in the tubes in the fragility test by smears in 1 case and found that the number of nucleated red cells was greatly increased in the more hypotonic solution. Thus it is possible that in cases of this type the circulating blood contains red cells of increased fragility, as well as cells of diminished fragility, with all intermediate degrees of osmotic resistance. However, in many cases of acquired hemolytic icterus the osmotic fragility of the red cells has been normal or but slightly increased even during a hemolytic crisis, while in other instances of the disease the striking alteration of the resistance of the red cells to hypotonic saline solutions present in 4 of my cases has not been observed. Thus it seems probable that in this disease the spherocytosis, the fragility of red cells and the degree of hemolysis are not so closely related as they are in congenital hemolytic anemia, in which increased fragility is constantly present. Furthermore, in acquired hemolytic anemia I have seen the osmotic fragility return to normal in a few days after splenectomy, while in the congenital type of the disease the increased fragility is little if at all reduced after removal of the spleen.

The theories concerning the relation of spheroidicity of the red cells and increased osmotic fragility are based chiefly on that relationship constantly present in congenital hemolytic anemia and apparently need revision if they are to apply to acquired hemolytic icterus, in which osmotic resistance may be either normal or greatly reduced. Thus in the latter disease the red cells are probably injured by a hemolysin which does not make them more fragile than normal in hypotonic saline solutions in every instance.

Widal and Abrami [8] expressed the belief that the hemolysin in acquired hemolytic icterus is almost completely attached to the red cells. Most of the complement in the serum would therefore be absorbed by this antigen-antibody union. Thus in vitro the serum would not be hemolytic, since all of the antibody would be immediately fixed by its antigen and the complementary power of the serum would

have diminished or would be absent since all of the complement would be fixed by the antigen-antibody combination. The red cells under such conditions would be completely dissolved if the amount of complement was sufficient. However, if the quantity of complement fixed by the antigen-antibody combination was too small, the red cells would show increased fragility. Thus in the presence of red cells and hemolysin, if a quantity of complement too small to produce hemolysis is added, the resistance of the red cells would be considerably diminished.

It is remarkable that in my cases and in the reported examples of acquired hemolytic anemia the osmotic fragility of the red cells, the degree of spheroidicity and the presence of autoantibodies or isoantibodies in the serum in vitro do not correlate with the degree of anemia or the rapidity of its development and any satisfactory theory of the genesis of acquired hemolytic icterus must be able to explain these apparent inconsistencies.

The size of the individual or of the average red cell was not determined in my cases. In general the smears showed some changes from time to time, depending on the stage of the disease. The acute phase was usually accompanied by marked evidences of increased regenerative activity, and many red cells in the circulation were larger than normal in contrast with the microspherocytes, which were constantly present in large numbers. During the process of recovery from the disease or after a hemolytic crisis both macrocytes and spherocytes disappeared or diminished in number slowly as the blood returned to normal or to a relatively quiescent phase of the disease. I got the impression from study of smears that the average diameter of the red cells was about normal. Macrocytes and spherocytes were present in all cases, and it seemed of little importance whether one called the anemia spherocytic, macrocytic, pseudomacrocytic, or normocytic with macrocytes and spherocytes. If such a classification is to be used, and its value is doubtful, I should prefer the term "pesudomacrocytic" as used by Dameshek and Schwartz [15] to designate the remarkable blood picture which has been a constant feature of acquired hemolytic anemia whether of acute or chronic type.

PATHOGENESIS

Many of the clinical and hematologic features of acquired hemolytic anemia may be present in certain infections, in many intoxications caused by chemicals and drugs, in anemia before and after parturition and in the course of each of a number of maladies in which hemolytic crises may occur, such as sickle cell anemia, congenital hemolytic anemia and chronic hemolytic anemia of unknown cause. However, after every diagnostic possibility has been explored, there are a few cases of acquired hemolytic anemia with strikingly similar clinical symptoms and hematologic findings for which no etiologic factor can be found and which cannot be classified in any other group of cases of hemolytic anemia. In this group one may assume that the hemolytic agent is formed within the body by some unknown and probably endogenous mechanism. There is always the probability that the acquired hemolytic anemia of this group may be further divided into different types as new etiologic factors are discovered or as new types of endogeneous hemolysins may be determined.

Acquired hemolytic icterus is apparently produced by the entrance into the blood stream of a hemolytic agent of unknown type and of unknown site of origin. This hemolysin may be the same autoantibody to the red cells which is often demonstrable in the serum of a patient with the disease, but at present the evidence does not support that assumption, since the autoantibody is not constantly present in the disease. However, its absence in vitro does not definitely exclude its possible

presence in vivo. I believe, as I shall discuss later, that the autoantibody is the result and not the cause of the disease.

This hemolytic agent, regardless of its nature or of its place of origin, apparently does not damage the spleen, the liver or the bone marrow since postmortem examination has failed to show any changes in these organs which cannot be explained by the presence of excessive hemolysis and profound anemia. In particular, I have not found any evidence of infection or intoxication of exogenous origin or any of the usual changes common to other known blood dyscrasias.

One may assume that the hemolytic agent damages the red cells only after they have entered the general circulation and that these damaged cells are not destroyed in the circulating blood, as they are in the various types of hemoglobinuria, although in the very acute, fulminating examples of the disease some hemoglobin may escape through the hepatolienal system to be excreted by the kidney. Thus large numbers of red cells injured by the hemolysin become spherocytes but continue to circulate in the blood stream. In some instances these damaged red cells show increased osmotic fragility but in other cases they have normal osmotic resistance. They eventually enter the spleen, where they are held back by some process not known at present. In the spleen the erythrostasis [22] constantly increases, and this, together with the normal destructive action of the spleen, leads to increasing hemolysis of the red cells previously damaged in the circulating blood. The spleen constantly enlarges from congestion, and evidences of the destruction of blood become intense.

Since there is no evidence of damage of the spleen in the disease, one may assume that some alteration of the red cells produces a change in their physical characteristics causing them to dam up in the spleen. Certain facts are important in this respect. The Ehrlich-Morgenroth phenomenon was present in a patient observed by Dameshek and Schwartz.[15] Hyaline thrombi were present in the peripheral arterioles of a patient studied by Moschcowitz [21] and have been observed in spleens removed at operation from other patients with the disease. These hyaline thrombi are produced by local agglutination of red cells in the smaller vessels. Thus a positive Ehrlich-Morgenroth phenomenon in this disease in which hemoglobinuria is a rare occurrence is, in my opinion, not proof that hemolysis in any considerable degree is taking place in the peripheral circulation. If it were, hemoglobinuria would be a more constant symptom. It seems probable that in acquired hemolytic anemia the red cells are injured in the blood stream, that if stasis is produced agglutination takes place with considerable ease and that then a certain degree of hemolysis of the conglutinated red cells occurs in situ. Erythrostasis in this disease is largely limited to the spleen, although a minimal amount of stasis, leading to intravascular hemolysis and the formation of hyaline thrombi, may take place in the peripheral arterioles. I am of the opinion that the erythrostasis in the spleen, by whatever change in the physical characteristics of the red cells it may be produced, is of considerable importance in the genesis of the disease. There is also considerable clinical evidence that it may be the cause of the formation of the antibody and of the remarkable type of osmotic fragility encountered in the red cells of some patients.

The hemolytic agent in acquired hemolytic anemia apparently injures susceptible red cells constantly but with varying degrees of intensity for a period. It then may disappear spontaneously, and the patient may recover completely. Thus a patient in an acute hemolytic crisis may recover without treatment or with only one or a very few small transfusions. This outcome has been reported especially frequently in those very young patients whose records have been published as those of Lederer's anemia. The hematologic data on many of these

patients have been incomplete, but in a number the alterations of the blood have been identical with those found in acquired hemolytic anemia. Furthermore, a number of these patients have recovered only after splenectomy. In contrast to my cases, however, the number of cures in the reported cases of Lederer's anemia has been so high that I suspect either that it may be a different type of hemolytic anemia, or that, more probably, some other factor is present to explain the discrepancy. Careful study of the cases reported by Lederer and other observers has convinced me that the disease is identical with acute acquired hemolytic anemia, although it is rather remarkable that the earlier references to the latter disease were not mentioned. Since Lederer's anemia was believed to be cured in every instance by transfusions and since each author reported one or at most a few instances of the disease it is possible that those patients who died and those patients whose hemolytic anemia recurred or became chronic were not reported as having the disease described by Lederer. At least in my experience the patient with acute acquired hemolytic anemia of unknown cause and with the characteristic changes of the blood which I have described is often not cured by either transfusions or splenectomy but instead has the disease in a chronic form after an apparently acute onset. The severity and the duration of the disease certainly vary greatly. In some instances a single small transfusion will produce a cure; in others splenectomy is necessary to save the patient's life, although it may not lead to a permanent cure. One patient reported by Widal and Abrami [8] had a spontaneous cure after having had hemolytic crises for twelve years.

The presence of increased osmotic fragility of the red cells together with jaundice and splenomegaly in acquired hemolytic anemia has doubtless occasioned confusion of this disease with the hemolytic crises of congenital hemolytic icterus. This error may be avoided by accurate observation of the close relatives of the patient and by careful morphologic study of the blood. In my experience acute hemolytic crises of the severity seen in acute or chronic acquired hemolytic anemia are rare in congenital hemolytic icterus. Furthermore, increased osmotic fragility is constantly present in the congenital type of the disease but was observed in less than half of my patients with acquired hemolytic anemia. However, increased osmotic fragility of the red cells is not proof that the disease in question is congenital hemolytic icterus as is usually stated in textbooks and in the hematologic literature.

The ultimate outcome of the disease is extremely variable. There is a group of patients with the acute type of the disease who are cured by transfusions or by splenectomy or may even show spontaneous healing. In a large number of patients who survive the acute phase of the disease the illness thereafter runs a chronic course interrupted by hemolytic crises of variable intensity. At any stage the disease may apparently heal spontaneously or it may be improved by splenectomy. However, I have seen several patients in whom splenectomy proved to be of no value. Other patients in whom the disease takes a chronic course present jaundice, anemia and frequent hemolytic crises. Some of these die of the anemia or of intercurrent infections. Some apparently die of a combination of anemia and hepatic insufficiency with marked fibrosis of the liver. Such patients whom I have seen have pigment stones in the gallbladder, in the common duct and in the hepatic ducts and also, frequently, innumerable small putty-like pigment stones in the intrahepatic biliary ducts. Thus acquired hemolytic anemia with constant jaundice eventually becomes complicated by obstructive jaundice and by fibrosis of the liver with increased portal pressure.

SUMMARY AND CONCLUSIONS

I have reported a series of cases of acute or chronic hemolytic anemia of the acquired type characterized by more or less rapid destruction of erythrocytes. Splenomegaly is constant, and it is probable that the destruction of blood occurs chiefly in the spleen. There is a pseudomacrocytic blood picture, usually with a high color index. Large numbers of macrocytes and microspherocytes are present in the blood film during the hemolytic crises in the acute type of the disease or constantly in the chronic type of the disease. The red cells may show extreme osmotic fragility, or they may be normally resistant to hypotonic saline solutions. This abnormality is not related to the number of spherocytes in the circulating blood.

The blood may or may not contain autoagglutinins or autohemolysins.

The disease is neither hereditary nor congenital, and no etiologic factor has been determined in any of the reported cases.

The acute type of the disease has been reported as Lederer's anemia. Subacute and chronic types are probably more frequent than is commonly believed.

The disease may heal spontaneously, or it may be cured by transfusions or by splenectomy. The more chronic types of the disease may or may not be cured by removal of the spleen. During the serious hemolytic crisis often seen in the disease removal of the spleen may be life saving even if it does not lead to complete cure.

THERAPEUTIC OBSERVATIONS IN CUSHING'S SYNDROME

EFFECT OF VARIOUS AGENTS ON CALCIUM, PHOSPHORUS AND NITROGEN EXCRETION IN A PATIENT WITH PITUITARY BASOPHILISM

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Skeletal decalcification has been recognized as a characteristic feature of pituitary basophilism since the syndrome was first described by Cushing, in 1932.[1] Such decalcification occurs likewise in those forms of Cushing's syndrome in which hyperplasia or tumor of the adrenal cortexes, rather than basophilic adenoma of the anterior lobe of the pituitary, is the dominant endocrine lesion. The demineralization of bone may be widespread but occurs chiefly in the skull, spine and pelvis. It may be so severe as to result in spontaneous or pathologic fractures, among which compression fractures of the vertebrae are common. Despite the long-recognized prominence of such skeletal demineralization, there have been comparatively few efforts to study the pathologic physiology of the process.

Freyberg and Grant [2] in 1936 reported detailed observations on a patient with a verified basophilic adenoma of the pituitary on whom studies of calcium, phosphorus and nitrogen metabolism were made under varying conditions of diet and medication. They reviewed the previous rather scant and inconclusive studies on calcium and phosphorus metabolism in Cushing's disease. They concluded from the study of their own case that despite the need for calcium and phosphorus these substances were not adequately absorbed. They further observed that large amounts of vitamin D, up to 200,000 U. S. P. units daily, did not facilitate the absorption of calcium and phosphorus but that calcium injected intravenously was apparently retained. They found no evidence to suggest that the parathyroids played any part in the process of demineralization and concluded that a complete understanding of the mechanism must await further study.

Bauer and Aub [3] reviewed the rather conflicting experimental evidence relating to the effect of the pituitary on calcium and phosphorus metabolism. They referred to a patient with Cushing's disease who was in distinctly negative calcium balance while on a low intake of calcium. After successful irradiation therapy, with subsidence of the syndrome, the degree of negativity of the calcium balance was greatly reduced. No striking abnormality in phosphorus balance was noted either before or after treatment.

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1. Cushing, H.: Basophile Adenomas, J. Nerv. & Ment. Dis. **76**:50 (July) 1932.

2. Freyberg, R. H., and Grant, R. L.: Calcium and Phosphorus Metabolism in a Verified Case of Pituitary Basophilism, Arch. Int. Med. **58**:213 (Aug.) 1936.

3. Bauer, W., and Aub, J. C.: Studies of Calcium and Phosphorus Metabolism: Influence of Pituitary Gland, J. Clin. Investigation **20**:295 (May) 1941.

In 1941 Albright and his associates [4] advanced the theory that many of the prominent features of Cushing's syndrome can be explained by assuming a hyperfunction of the adrenal cortex leading to increased gluconeogenesis from protein. This, they felt, could explain not only the diabetes but the muscular weakness, capillary fragility, cutaneous changes and osteoporosis, all of the latter being the result of a decreased supply of the protein necessary to the normal components of muscle, capillary walls, skin and the osteoid or bony matrix on which the mineral elements of bone are deposited. This theory would lead to the inference that the demineralization of bone in Cushing's syndrome is the result of an inadequate tissue framework for the deposition of calcium and phosphorus compounds rather than of an increased active withdrawal of calcium and phosphorus from the bones, such as occurs, for instance, in hyperparathyroidism. Albright and his associates included in their report the effect of estrogen, progesterone and testosterone propionate on calcium, phosphorus and nitrogen balance in their patients with Cushing's disease. One of their patients was in positive calcium balance and 1 in approximate calcium equilibrium before treatment was begun. One patient was in negative phosphorus balance and 1 in approximate phosphorus equilibrium before treatment. The administration of estrogen was followed by a temporary negative calcium balance due to increased fecal loss of calcium in at least 1 patient. Testosterone propionate produced retention of calcium with sharp reduction in urinary calcium, in 2 patients. There was likewise retention of phosphorus and nitrogen following testosterone therapy. General clinical improvement was reported to have followed the development of positive nitrogen and phosphorus balances in all of their patients.

In 1941 we encountered a patient with the classic picture of Cushing's syndrome on whom it was possible to make prolonged metabolic studies. Such studies were made at intervals from February 1941 until April 1942 with the following purposes in mind: (1) to observe the effects of varying calcium-phosphorus ratios in the diet and of various combinations of therapeutic agents on the excretion of calcium, phosphorus and nitrogen; (2) to determine the effect of such dietary and therapeutic combinations on the serum concentrations of calcium, inorganic phosphorus and protein and the activity of phosphatase in the serum, and (3) to observe the effect of such treatment on the patient's symptoms and clinical course.

The therapeutic agents employed included estrogens given orally and parenterally; testosterone propionate by intramuscular injection; calcium and large doses of calciferol (vitamin D_2). These substances were administered in varying combinations.

REPORT OF A CASE

Miss G. S., a school teacher aged 30 years, was referred to the Hospital of the University of Pennsylvania Feb. 18, 1941, by Dr. Chalmers Montgomery, of Altoona, Pa. Her chief complaint was pain in the back of seven weeks' duration. Her past medical history had been entirely irrelevant until the age of 26. At that time (May 1937) her menses, which previously had been normal and regular since their onset, at the age of 13 years, became increasingly scant and irregular. They finally ceased altogether in May 1938. At about the same time she gained 10 pounds (4.5 Kg.), which was deposited chiefly about the face, hips and abdomen. Increasing facial hirsutism appeared, with acneform lesions on the face, neck and back. In the summer of 1937 ecchymotic areas began to appear on the legs without trauma, and these had continued to recur until the time of her admission to the hospital. Episodes of renal colic with the passage of calculi occurred, one in the autumn of 1938, one in March 1939 and one in June and July 1940. Hypertension of varying degree had been noted since June 1939. In the summer of 1940 transitory swelling, redness and burning of both legs

4. Albright, F.; Parson, W., and Bloomer, E.: Cushing's Syndrome, Interpreted as Hyperadreno-Corticism Leading to Hypergluconeogenesis: Results of Treatment with Testosterone Propionate, J. Clin. Endocrinol. **1**:375 (May) 1941.

occurred. This was followed by polydypsia and polyuria, and sugar was found in the urine in August 1940. Since that time her diet had been restricted in carbohydrate content, and she had received regular doses of insulin. She had noted progressive muscular weakness, dryness and thinning of the skin and two episodes of transitory pain and stiffness in the hips. She had been obliged to stop teaching in the summer of 1940 and had become increasingly depressed and anxious about her condition. Between October and December 1939 she received 418 roentgens (r) of irradiation to the right temporal region and 424 r to the left temporal region. Seven weeks before her first admission to the hospital she had suffered a sharp lumbar pain while attempting to open a window, and since that time she had been increasingly disabled by backache and muscular weakness, so that she was scarcely able to walk or sit erect when she entered the hospital. Physical examination showed rather pronounced

Fig. 1.—*A*, the patient as she appeared before treatment; *B*, the face of the patient, showing hirsutism following the prolonged use of testosterone.

facial hirsuties and extensive acne, involving the face, neck and upper part of the back. The complexion was ruddy, and the skin was thin and parchment-like, with numerous purplish red striae over the thighs and the lower part of the abdomen (fig. 1 *A*). Ecchymoses in varying stages of absorption were present over the legs. There was slight edema of the ankles. The patient was not obese, weighing 120 pounds (54.4 Kg.) and being 5 feet 1 inch (155 cm.) in height. However, relaxation of the abdominal muscles gave a false impression of abdominal obesity. The breasts were atrophic. Pelvic examination showed some vulvar irritation and a small uterus. The blood pressure varied from 180 to 190 systolic and from 110 to 115 diastolic. Further studies revealed the following: The basal metabolic rate was —18 per cent; the cholesterol content of the serum was 312 mg. per hundred cubic centimeters, the inorganic phosphorus content 3.1 mg. and the calcium content 10.3 mg. The fasting

blood sugar level was 107 mg. per hundred cubic centimeters and the urea nitrogen content 10 mg. The serum magnesium content was 2 milliequivalents per liter. The urinary excretion of 17-keto steroids was within normal limits (13 mg. in twenty-four hours). The protein content of the serum was 5.2 Gm. per hundred cubic centimeters; the serum phosphatase activity, 4.6 Bodansky units; the carbon dioxide-combining power, 69 volumes per cent; total base, 146.9 milliequivalents per liter, and chloride, 101 milliequivalents per liter. The hemoglobin content was 17.3 Gm. per hundred cubic centimeters. There were 5,660,000 red blood cells, 15,000 white blood cells and 331,000 platelets per cubic millimeter. The prothrombin time and the fragility of the red cells were normal. The volume of serum was 43.3 cc. per kilogram of body weight, which is within the normal range of values for serum volume in this laboratory (normal 40 to 46 cc. per kilogram). The urinalyses showed intermittent glycosuria, and the tolerance for dextrose was definitely impaired, the blood sugar reaching 315 mg. per hundred cubic centimeters one hour after the first administration of dextrose (two dose method of Exton and Rose) (table 1). Roentgen examination of the skeleton showed marked demineralization involving the skull, parts of the cervical, thoracic and lumbar portions of the spine, the pelvis and the ribs. Old fractures of several ribs and of several thoracic and lumbar vertebrae and fractures of the pubic and ischial rami were noted. There was no evidence of enlargement of the sella turcica. The visual fields were full, and the ocular fundi showed only some arterial constriction. Intravenous urograms revealed functioning kidneys without evidence of deformity or of calculus formation. Examination of the adrenal areas following perinephric injection of air was first reported by the roentgenologist, Dr. E. P. Pendergrass, to show a shadow suggestive of enlargement of the right adrenal. A subsequent examination led, however, to some qualification of the original opinion, and it was finally concluded that a definite roentgen diagnosis of adrenal enlargement could

TABLE 1.—*Results of Dextrose Tolerance Tests*

Date	Blood Sugar, Mg. per 100 Cc.		
	Fasting	One-Half Hour	One Hour
3/6/41	130	281	315
5/23/41	70	212	246
10/24/41	70	130	100
4/8/42	116	198	218

not be made. Roentgenograms of the chest showed no evidence of substernal enlargement of the thyroid or thymus. The cardiac shadow was slightly increased in size, and the electrocardiogram showed left axis deviation. The patient, in short, presented an almost classic picture of Cushing's syndrome with the sole exception that she lacked somewhat the characteristic "buffalo type" of obesity about the shoulders and upper part of the trunk. Demineralization of the skeleton was unusually extensive and severe, and the changes in the skin were striking. Because of the questionable findings in the region of the right adrenal following perinephric injections of air and roentgen examination, it was felt that surgical exploration of the adrenals was indicated. The patient was therefore operated on by Dr. E. L. Eliason on May 28, 1941, after a period of study from March 13 to May 24 (table 2). The left adrenal was explored through a posterior incision and was found to be grossly normal. An anterior incision of the right side was then made, through which the right adrenal, the ovaries and the uterus were explored. These organs were all normal, although the right adrenal was slightly larger than the left. Biopsy sections were taken from both adrenals but showed only normal structure.

The patient was given a measured diet of known calcium, phosphorus and nitrogen content, which was maintained without variation during the various phases of study. All urine and feces were collected and separately pooled into three day lots. The limits of each three day period of collection of feces were marked by the appearance of carmine in the stool. The concentrations of calcium, inorganic phosphorus and protein in the serum were measured at intervals which varied according to the nature of the therapeutic agents employed. The methods used for the determination of protein in the serum and of calcium and inorganic phosphorus in the serum, feces and urine were identical with those referred to in a previous communication.[5] The nitrogen content of the diet, urine and feces was determined by the

5. Rose, E.; Perloff, W. H., and Sunderman, F. W.: The Effect of Low Calcium Diet and Calciferol (Vitamin D_2) on Calcium and Phosphorus Metabolism: Studies on Two Parathyreoprivic Patients and One "Normal" Subject, Am. J. M. Sc. **202**:691 (Nov.) 1941.

TABLE 2.—*Summary of Data on Metabolism and Therapy*

Three Day Periods Beginning March 13, 1941	Therapy	Weight, Pounds	Calcium, Gm.					Phosphorus, Gm.					Nitrogen, Gm.				
			Intake	Excretion			Balance	Intake	Excretion			Balance	Intake	Excretion			Balance
				Urine	Feces	Total			Urine	Feces	Total			Urine	Feces	Total	
I	.....	116½	3.0	0.783	2.016	2.799	+0.201	2.40	0.726	0.812	1.538	−0.862	32.1	21.6	3.2	24.8	+7.3
II	.....	116½	3.0	0.427	2.952	3.379	−0.379	2.40	0.600	0.951	1.551	+0.849	32.1	21.0	4.1	25.1	+7.0
III	.....	116¾	3.0	0.617	1.740	2,357	+0.643	2.40	0.617	1.092	1.709	+0.691	32.1	24.7	3.0	27.7	+4.4
IV	.....	.....	0.480	0.553	1,278	1.831	−1.351	2.40	0.670	1.491	2.161	+0.239	32.1	25.0	3.5	28.5	+3.6
V	.....	117	0.480	0.829	0.252	1.081	−0.601	2.40	0.640	1.000	1.640	+0.760	32.1	27.6	3.3	30.9	+1.2
VI	.....	.....	0.480	0.747	0.350	1.097	−0.617	2.40	0.725	1.110	1.835	+0.565	32.1	29.1	4.2	33.3	−1.2
VII	.....	115	0.480	0.660	0.375	1.035	−0.555	2.40	0.637	1.080	1.717	+0.683	32.1	28.6	4.0	32.6	−0.5
VIII	60 cc. Ca Gluc. I.V. (.513 Gm.)	.....	2.019	1.383	0.350	1.733	+0.285	2.40	0.659	1.010	1.664	+0.736	32.1	28.9	3.9	32.8	−0.7
IX	60 cc. Ca Gluc. I.V. (.513 Gm.)	115	2.019	1.255	0.410	1.665	+0.353	2.40	0.566	1.240	1.806	+0.594	32.1	25.8	4.2	30.0	+2.1
X	1.66 mg. estradiol benzoate daily I.M.	116½	3.0	0.796	2.156	2.952	+0.048	2.40	0.746	1.034	1.780	+0.620	32.1	28.5	0.06†	....	.....
XI	1.66 mg. estradiol benzoate daily I.M.	116½	3.0	0.719	1.845	2.564	+0.436	2.40	0.637	0.820	1.457	+0.943	32.1	25.2	1.7	26.9	+5.2
XII	1.66 mg. estradiol benzoate daily I.M.	118½	3.0	0.586	2.160	2.746	+0.254	2.40	0.528	0.968	1.496	+0.904	32.1	21.9	2.3	24.2	+7.9
XIII	1.66 mg. estradiol benzoate daily I.M.	117	3.0	0.445	2,928	3,373	−0.373	2.40	0.451	1.478	1.929	+0.471	32.1	17.9	2.3	20.2	+11.9
XIV	1.66 mg. estradiol benzoate daily I.M.	115	3.0	0.847	3.174	4.021	−1.021	2.40	0.905	1.196	2.101	+0.299	32.1	30.7	2.0	32.7	−0.6
XV	1.66 mg. estradiol benzoate daily I.M.	117	3.0	0.842	1.982	2.824	+0.176	2.40	0.731	1.102	1.833	+0.567	32.1	25.9	1.9	27.8	+4.3
XVI	25 mg. testosterone propionate daily I.M.	117½	3.0	0.730	2.145	2.865	+0.135	2.40	0.726	1.235	1.961	+0.439	32.1	24.9	3.3	28.2	+3.9
XVII	25 mg. testosterone propionate daily I.M.	118½	3.0	0.551	3.060	3.611	−0.611	2.40	0.486	1.122	1.608	+0.792	32.1	21.2	2.8	24.0	+8.1
XVIII	25 mg. testosterone propionate daily I.M.	119	3.0	0.514	3.399	3.913	−0.913	2.40	0.356	1.584*	1.940	+0.460	32.1	19.1	2.7*	21.8	+10.3
XIX	25 mg. testosterone propionate daily I.M.	.....	3.0	0.619	2.991	3.610	−0.610	2.40	0.232	1.056	1.288	+1.112	32.1	20.1	1.9	22.0	+10.1
XX	25 mg. testosterone propionate daily I.M.	120	3.0	0.472	2.295	2.767	+0.233	2.40	0.434	0.990	1.424	+0.976	32.1	15.5	2.3	17.8	+14.3
XXI	400,000 units Vitamin D_2	121	3.0	0.595	1.800	2.395	+0.605	2.40	0.584	0.735	1.319	+1.081	32.1	21.4	1.6	23.0	+9.1
XXII	400,000 units Vitamin D_2	121	3.0	0.345	1.870	2.215	+0.785	2.40	0.429	1.172	1.611	+0.789	32.1	22.6	3.4	26.0	+6.1
XXIII	400,000 units Vitamin D_2	120½	3.0	0.335	1.116	1.451	+1.549	2.40	0.086	0.666	1.351	+1.049	32.1	25.3	1.9	27.2	+4.9
XXIV	400,000 units Vitamin D_2	122½	3.0	0.347	0.960	1.307	+1.693	2.40	0.691	0.644	1.245	+1.155	32.1	22.1	2.1	24.2	+7.9
	Patient out of hospital for 123 days. During this time she received 4 Gm. of calcium gluconate and 50,000 U.S.P. units of vitamin D_2 daily by mouth and 25 mg. of testosterone propionate daily by intramuscular injection.																
Beginning Oct. 15, 1941																	
I	50,000 U.S.P. units vitamin D_2 daily and 25 mg. of testosterone propionate I.M.	118	3.0	0.671	1.505	2.176	+0.812	2.40	0.589	0.899	1.488	+0.912	32.1	26.4	4.5	30.9	+1.1
II	50,000 U.S.P. units vitamin D_2 daily and 25 mg. of testosterone propionate I.M.	117½	3.0	0.670	2.141	2.811	+0.177	2.40	0.541	0.940	1.481	+0.919	32.1	20.0	4.2	24.2	+7.83
III	50,000 U.S.P. units vitamin D_2 daily and 25 mg. of testosterone propionate I.M.	118	3.0	0.786	2.284	3.064	−0.076	2.40	0.489	1.000	1.489	+0.911	32.1	23.5	5.0	28.5	+3.57
	Patient out of hospital 59 days. During this time she received 4 Gm. of calcium gluconate and 50,000 units vitamin D_2 daily by mouth.																
Beginning Dec. 13, 1941																	
I	50,000 units vitamin D_2 daily	108	3.0	1.006	1.918	2.924	+0.076	2.40	0.908	0.928	1.836	+0.564	32.1	30.5	4.5	35.0	−2.9
II	50,000 units vitamin D_2 daily	108	3.0	1.003	2.097	3.100	−0.100	2.40	0.912	0.908	1.820	+0.580	32.1	28.2	4.8	33.0	−0.9
III	50,000 units vitamin D_2 daily	107	3.0	0.980	1.638	2.168	+0.382	2.40	0.935	0.761	1.695	+0.705	32.1	28.8	4.2	33.0	−0.9
	Patient out of hospital 67 days. During this time she received 4 Gm. calcium gluconate, 50,000 units vitamin D_2 and 1 mg. stilbestrol daily by mouth.																
Beginning March 24, 1942																	
I	Stilbestrol 1 mg. Calciferol 50,000 units of vitamin D_2 daily	110½	3.0	0.940	2,420	3.360	−0.360	2.40	0.657	1.454	2.111	+0.289	32.1	22.9	4.1	27.0	+5.1
II	Stilbestrol 1 mg. Calciferol 50,000 units of vitamin D_2 daily	110½	3.0	0.947	2.216	3.163	−0.163	2.40	0.776	1.332	2.108	+0.292	32.1	25.4	4.4	29.8	+2.3
III	Stilbestrol 1 mg. Calciferol 50,000 units of vitamin D_2 daily	109	3.0	0.970	1.655	2.625	+0.375	2.40	0.889	1.157	2.046	+0.354	32.1	24.1	3.8	27.9	+4.2
IV	Stilbestrol 1 mg. Calciferol 50,000 units of vitamin D_2 daily	110	3.0	1.042	2.398	3.440	−0.440	2.40	0.774	1.678	2.452	−0.052	32.1	24.3	4.9	29.2	+2.9

* Calculated on 2/2 of two day specimen.
† Specimen considered

Kjeldahl method. Hashed samples of the daily diet were prepared and analyzed for total calcium, phosphorus and nitrogen content. The daily diet was found to contain 156 mg. of calcium, 800 mg. of phosphorus and 10.69 Gm. of nitrogen. All rejected food was weighed, and the calculated loss in calcium, phosphorus and nitrogen content was deducted from the daily intake. Deficiencies in intake of calcium were compensated for, when desired, by the addition of weighed amounts of calcium lactate.

Between March 13, 1941 and April 2, 1942, studies were made during four separate admissions to the hospital. The significant data relating to the time and duration of the periods of study, the therapy and the dietary intake of calcium, phosphorus and nitrogen are shown in table 2. On each admission to the hospital the collections of urine and feces were not begun until at least six days after the institution of the measured diet. Changes in the concentration of calcium, inorganic phosphorus and protein in the serum and the excretion of calcium, phosphorus and nitrogen in the urine and feces are shown in figures 2 and 3.

The significant data in these figures may be summarized as follows:

Serum Calcium.—The calcium content of the serum remained within normal limits throughout. The initial level was near the lower limit of normal (9.4 mg. per hundred cubic centi-

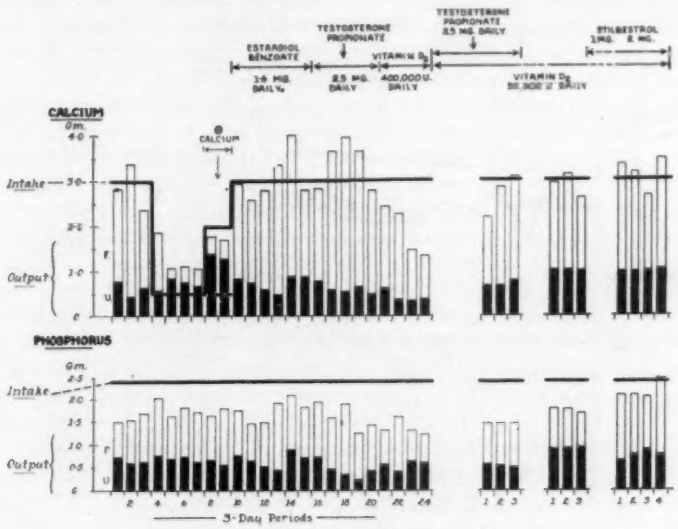

Fig. 2.—Data on metabolic studies.

meters). Slight rises in the serum calcium were observed following the ingestion of 1 Gm. of calcium per day, the intravenous injection of calcium gluconate and large oral doses of vitamin D_2. After the prolonged administration of calcium, vitamin D_2 and testosterone propionate, the calcium concentration of the serum reached its highest level, of 10.7 mg. per hundred cubic centimeters. It should be noted, however, that the serum protein concentration was also increased at this time.

Serum Inorganic Phosphorus.—There was a moderate rise in the level of inorganic phosphorus in the serum following the intravenous administration of calcium and a slight rise which began after the administration of testosterone propionate and continued after use of large doses of vitamin D_2 was begun.

Excretion of Calcium (fig. 2).—When the intake of calcium per three day period was 3 Gm. and that of phosphorus was 2.4 Gm., the patient was in approximate calcium equilibrium. When the intake was reduced to 0.48 Gm. per three day period, a negative calcium balance developed, the output in the urine alone exceeding the intake. When approximately 3 Gm. of calcium, three quarters of which was administered intravenously, was given per three day period, the patient retained calcium to a moderate degree despite a sharp rise in urinary excretion of calcium. The administration of large daily doses of estradiol benzoate was not accompanied with any significant change in the pattern of calcium excretion, two

phases of retention being separated by a brief interval of loss. During three of the five periods, in which large doses of testosterone were given, there was a significant loss of calcium, chiefly in the feces. During these three periods the amount of calcium lost through fecal excretion equaled or exceeded the amount ingested. The administration of large doses of vitamin D_2 was followed promptly by a pronounced retention of calcium, which was reflected in a decrease in both urinary and fecal excretion. After one hundred and twenty-three days of therapy with testosterone propionate, calcium gluconate and vitamin D_2 combined, there was retention of calcium in two of the three periods of study. No significant change occurred in calcium balance following the further administration of calcium gluconate and vitamin D_2 without testosterone. Following the administration of diethylstilbestrol, calcium gluconate and vitamin D_2 there was a negative calcium balance in three of the four periods of study.

Excretion of Phosphorus.—The patient remained in positive phosphorus balance throughout the course of our studies except in the final period, following administration of diethylstilbestrol. There was a slight trend toward increased retention following the administration of testosterone, which was maintained during the administration of large doses of vitamin D_2. Following prolonged therapy with testosterone, calcium gluconate and vitamin D_2, the degree

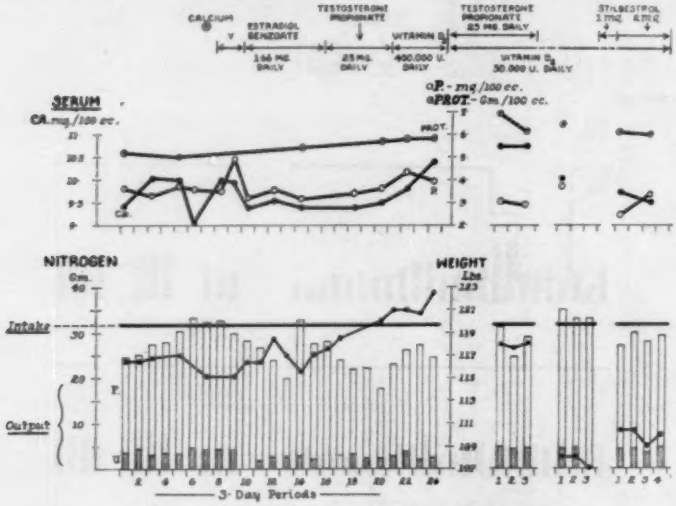

Fig. 3.—Data on metabolic studies.

of phosphorus retention was no greater than it had been without any therapy. After the withdrawal of testosterone, however, there was a slight increase in excretion of phosphorus, which occurred chiefly in the urine. After the prolonged administration of diethylstilbestrol orally, the excretion of phosphorus reached its peak; this increase occurred in the feces.

Excretion of Nitrogen (Fig. 3).—Fecal excretion of nitrogen varied between 2 and 4 Gm. per period. The significant variations in excretion were therefore chiefly in the urine. Before therapy was begun, the patient was in positive nitrogen balance, although the degree of retention decreased progressively. The administration of estradiol benzoate was followed by a progressive increase in retention of nitrogen except for one isolated period of increased excretion toward the end of the estradiol therapy. A somewhat similar increase in retention of nitrogen followed the administration of testosterone, but this became less marked when large doses of vitamin D_2 were given. After prolonged therapy with testosterone, calcium gluconate and vitamin D_2, there was only slight or moderate retention of nitrogen. After the withdrawal of testosterone there was consistent slight loss of nitrogen. After the administration of diethylstilbestrol, nitrogen was retained.

Weight.—The patient's weight varied from 107 to 122 pounds (48.5 to 55.3 Kg.). Minor variations occurred without obvious cause, but in general the weight tended to vary inversely with the loss of nitrogen.

Phosphatase activity in the serum increased from 4.6 to 8 Bodansky units after the completion of the first five periods of testosterone therapy and while the patient was receiving large doses of vitamin D_2, in May 1941. At this time, the concentration of calcium in the serum was higher than before treatment was started and nitrogen retained amounted to about 7 Gm. per period. The tolerance for dextrose showed a definite improvement after the prolonged treatment with testosterone propionate, calcium gluconate and vitamin D_2 (see table 1, 10/24/41). The dextrose tolerance curve, however, subsequently returned toward the original level. The concentration of protein in the serum rose from a low level of 5 Gm. per hundred cubic centimeters before treatment to 5.8 Gm. after the first five periods of testosterone therapy and subsequently to 6.9 Gm. after prolonged treatment with testosterone propionate, calcium gluconate and vitamin D_2. The values thereafter remained within normal limits.

COMMENT

Certain striking objective and subjective changes occurred during the course of our patient's treatment. The subjective changes included a definite increase in muscular strength and improvement in the backache following the prolonged period (one hundred and twenty-three days) (see table 2) of treatment with calcium gluconate, vitamin D_2 and testosterone. At the same time there was noted deepening of the voice, enlargement of the clitoris and marked increase in the facial acne and hirsutism (fig. 1 *B*). The hirsutism decreased when use of testosterone was stopped. The objective changes noted after prolonged testosterone therapy included amelioration of the diabetes with improvement in the tolerance for dextrose (table 1, Oct. 24, 1941) and some recalcification of the spine and increase in the urinary excretion of 17-keto steroids to 25 mg. per twenty-four hours.

Other definite objective changes may be listed as follows: (1) loss of calcium, chiefly through the urine, when the calcium intake was low; (2) ability to retain intravenously administered calcium; (3) retention of calcium and increased retention of phosphorus following large doses of vitamin D_2; (4) retention of nitrogen during and after the first phase of testosterone therapy, whereas less marked retention of nitrogen was noted following its continued use for a period of one hundred and twenty-three days, and (5) negative calcium balance, increase in fecal phosphorus and retention of nitrogen after the administration of diethylstilbestrol.

The striking improvement in muscular power, the recalcification of the spine and the apparent amelioration of the diabetes which followed prolonged testosterone therapy, as well as the retention of nitrogen which followed the first brief phase (fifteen days) of testosterone therapy confirm the observations regarding the beneficial effect of such treatment reported by Albright and his associates.[4] The increase in hirsutism and acne, the deepening of the voice and the enlargement of the clitoris which also followed this treatment must not be forgotten, however.

Our observations do not agree with those of Albright and his associates in the following respects: (1) Our patient was not in negative nitrogen or calcium balance before treatment was started; and (2) the retention of nitrogen and phosphorus which followed prolonged testosterone therapy was far from striking and was, in fact, no greater than the retention of these substances noted on several occasions before use of testosterone was begun.

Our observations agree with those of Freyberg and Grant in that our patient was able to retain intravenously injected calcium. Contrary to their findings, however, our patient was able to absorb calcium and phosphorus even when the calcium-phosphorus ratio in the diet was low. Furthermore, our patient, unlike theirs, showed a marked retention of calcium and phosphorus following the administration of large doses of vitamin D_2.

Adequate data pertaining to calcium, phosphorus and nitrogen metabolism have been reported in only a few cases of Cushing's syndrome. Discrepancies between

observations of various investigators cannot yet, therefore, be subjected to statistical analysis. An explanation of these discrepancies might lie in the possibility that the metabolic aberrations associated with the disease may not maintain a constant plateau of intensity. If, for example, the intensity of the basophilic pituitary or adrenal cortical dysfunction could be assumed to vary spontaneously from time to time, it might logically be inferred that variations in nitrogen, calcium and phosphorus balance would result, as well as variations in the severity of the diabetes. The ability to retain calcium, phosphorus and nitrogen as an effect of various forms of therapy might therefore vary considerably depending on the stage of the disease in which such phenomena were studied. This possibility is supported, to some extent, by the spontaneously changing trend in nitrogen excretion observed in our patient before treatment was begun (see fig. 2) and by the difference in calcium, phosphorus and nitrogen balance observed in the cases of Freyberg and Grant and of Albright and his associates under similar circumstances.

The history of the passage of renal calculi by our patient on four occasions between the autumn of 1938 and the summer of 1940 suggests that during this period she may have been excreting relatively large amounts of calcium and phosphorus in the urine. Diversion of ingested calcium and phosphorus or withdrawal of these substances from her skeleton may have occurred to a greater degree during this time than when she came under our observation.

Finally, some speculation may be permissible regarding the nature of skeletal decalcification in Cushing's syndrome.

The following possible mechanisms require examination:

1. Increased withdrawal of calcium and phosphorus from the bones. This might occur as the result of (*a*) parathyroid hyperfunction either resulting from pituitary stimulation or secondary to a renal lesion; (*b*) direct action of the pituitary, as postulated by Bauer and Aub in acromegaly,[3] or (*c*) hyperthyroidism. No evidence of primary or secondary hyperparathyroidism in Cushing's syndrome is available. The possibility of some direct effect of pituitary or adrenal cortical action on the calcium and phosphorus content of the skeleton in Cushing's syndrome can neither be proved nor disproved at present. Hyperthyroidism is not a feature of Cushing's syndrome and was not present in our patient.

2. Increased urinary excretion of calcium as the result of an intrinsic renal lesion[6] or acidosis.[7] No evidence of either of these conditions has been reported to date in Cushing's syndrome.

3. Inadequate absorption of calcium and/or phosphorus resulting either from an insufficient dietary supply or a lack of vitamin D or from some defect in the mechanism of intestinal absorption. The observations of Freyberg and Grant are the only ones we have been able to find which suggest inadequate absorption of calcium and phosphorus. Our own observations certainly do not confirm this. Our patient's diet was not deficient in calcium, phosphorus or vitamin D prior to her admission to the hospital.

4. The demineralization might be similar to that described as occurring after the menopause,[8] since amenorrhea usually occurs early in Cushing's syndrome. The

6. Albright, F.; Consolazio, W. V.; Coombs, F. S.; Sulkowitch, H. W., and Talbott, J. H.: Metabolic Studies and Therapy in Case of Nephrocalcinosis with Rickets and Dwarfism, Bull. Johns Hopkins Hosp. **66**:7 (Jan.) 1940.

7. Atchley, D. N.; Loeb, R. F.; Richards, D. W., Jr.; Benedict, E. M., and Driscoll, M. C.: On Diabetic Acidosis: Detailed Study of Electrolyte Balances Following Withdrawal and Re-Establishment of Insulin Therapy, J. Clin. Investigation **12**:297 (March) 1933.

8. Albright, F.; Smith, R. H., and Richardson, A. M.: Postmenopausal Osteoporosis: Its Clinical Features, J. A. M. A. **116**:2465 (May 31) 1941.

history of urinary lithiasis in our patient is reminiscent of similar transitory periods of formation of renal calculi in the earlier phases of so-called menopausal osteoporosis. However, our patient failed to retain calcium consistently while receiving large doses of estradiol benzoate and was actually in negative calcium balance with an increased fecal excretion of phosphorus after the prolonged oral administration of diethylstilbestrol. Furthermore, to relate the demineralization of Cushing's syndrome to that of the menopause is simply to label it without explaining it, since the basic mechanism of so-called menopausal osteoporosis is not yet understood.

5. Inability to lay down calcium and phosphorus compounds in the skeleton because of a defect in osteoid framework or matrix. This is the explanation suggested by Albright and his associates.[4] It assumes a deficient supply of protein for the formation of normal matrix because of abnormal diversion of protein for gluconeogenesis. This explanation implies that the bony defect is an osteoporosis rather than an osteomalacia.[9] Some support for this theory is contained in the studies reported by Albright and his associates [4] and is likewise offered by the subjective improvement and vertebral recalcification observed in our patient following the administration of testosterone and the failure of such improvement to progress after the withdrawal of this substance.

On the other hand, the following observations noted in our case argue somewhat against this theory.

(a) Our patient was not in negative nitrogen or phosphorus balance prior to the beginning of treatment, although she was diabetic.

(b) Retention of neither nitrogen nor calcium was marked after prolonged treatment with testosterone, calcium and vitamin D_2.

(c) Our patient was able to retain intravenously injected calcium without striking change in nitrogen balance. She also retained calcium after large doses of vitamin D_2 at a time when retention of nitrogen was declining. The fact that the serum calcium did not increase significantly during either of these phases suggests that the retained calcium may have been deposited, at least temporarily, in the bones.

If this theory is correct, one would expect to find osteoporosis in a variety of conditions when there is too little protein available for the formation of bony matrix. These would include chronic deprivation of protein; conditions associated with chronic loss of nitrogen, such as prolonged fevers and hyperthyroidism, and disorders in which prolonged hypoproteinemia exists, such as nephrosis and chronic hepatic disease. We have been able to find little evidence relating protein deprivation to osteoporosis. Malan [10] reported the production of atrophy of bone and osteoporosis in pigs by diets low in protein. He commented on the paucity of experimental data regarding the effect on skeletal structure of diets deficient in organic components.

Conner, Kao and Sherman [11] studied the effect of varying proportions of dietary protein and calcium on the body and skeletal growth and the total body calcium content of rats. They concluded that there was no consistent evidence that the increased gain in body weight which resulted from the higher levels of protein in

9. Albright, F.; Bloomberg, E., and Smith, P. H.: Postmenopausal Osteoporosis, Tr. A. Am. Physicians **55**:298, 1940.

10. Malan, A. L.: Diet and Osteomalacic Diseases in Domestic Animals, South African M. J. **14**:261 (July) 1940.

11. Conner, R. T.; Kao, H. C., and Sherman, H. C.: Further Studies on Relationship of Plane of Protein Intake to Rate of Normal Calcification During Growth, J. Biol. Chem. **138**:835 (June) 1941.

the diet had any accelerating effect on skeletal development as reflected in the percentage of body calcium. Rhoads and Kasinskas [12] found that callus formation after experimental fracture was delayed in dogs rendered hypoproteinemic by low protein diets and plasmapheresis. However, they did not report serum calcium values for their animals. Prolonged protein deprivation in the adult as seen clinically is not associated with osteoporosis. Of the conditions associated with prolonged loss of nitrogen, hyperthyroidism and possibly acromegaly are the only ones in which osteoporosis or decalcification occurs with significant frequency, and in these diseases there may well be other factors responsible. The hypoproteinemia of chronic nephrosis does not seem to produce skeletal decalcification. It is true that hepatic disease and chronic gastrointestinal disorders have been reported in association with severe skeletal changes,[13] but the pathologic physiology in these conditions is so complex that protein deficiency alone can scarcely be blamed with reason.

The possibility exists that the skeletal decalcification in Cushing's disease may be associated with some chronic impairment of hepatic function, although symptoms of disease of the liver are not characteristic of the syndrome. Studies of hepatic function in pituitary basophilism have not been reported. Although the protein level of the serum was low in our patient at times, a recent test of her hepatic function by the bromsulphalein method was normal.

It seems reasonable to conclude that the theory of protein deficiency as the basis of the osteoporosis of Cushing's disease still lacks proof, although some evidence in its favor exists.

SUMMARY

The case of a 30 year old woman with pituitary basophilism in whom skeletal changes were particularly striking and in whom the diagnosis was reached by exclusion is reported. Studies of the concentration of calcium, phosphorus, protein and phosphatase in the serum, the dextrose tolerance and the excretion of calcium, phosphorus and nitrogen before and after the use of various therapeutic agents and with diets of varying calcium content are reported. The therapeutic agents employed included estradiol benzoate, testosterone propionate, vitamin D_2, calcium gluconate and lactate and diethylstilbestrol, in varying combinations. Subjective and objective responses to treatment are described, and our observations are compared with those in similar studies reported by others. The possibility is mentioned that spontaneous variations in the intensity of the various metabolic aberrations in Cushing's syndrome may explain some of the discrepancies in the studies reported to date. Several possible explanations of the skeletal decalcification characteristic of the syndrome are briefly considered. It is concluded that no completely satisfactory explanation of the skeletal demineralization in Cushing's disease is yet available.

ADDENDUM

Further irradiation therapy was given to the pituitary and parathyroid areas in our patient between April 1 and 16, 1942. The patient has recently returned for further observation, which was carried out in the hospital from Aug. 6 to Aug. 15, 1942. Between April 22, 1942 and this admission the patient had received 25 mg. of testosterone propionate twice weekly by intramuscular injection and had also taken by mouth 2 mg. of diethylstilbestrol, 4 Gm. of

12. Rhoads, J. E., and Kasinskas, W.: The Influence of Hypoproteinemia on the Formation of Callus in Experimental Fracture, Surgery **11**:38 (Jan.) 1942.

13. Ask-Upmark, E.: Osteomalacia hepatica, Acta med. Scandinav. **99**:204, 1939. Mentha, C.: Ostéodystrophies pancréatiques humaines et expérimentales, Schweiz. Ztschr. f. allg. Path. u. Bakt. **4**:209, 1941. Sikl, H.: Osteomalacie bei langdauernder Erkrankung der Gallenwege, Frankfurt. Ztschr. f. Path. **55**:120, 1941.

calcium gluconate and 100,000 U. S. P. units of vitamin D_2 daily. Ten units of protamine zinc insulin and 10 units of unmodified insulin had been injected daily. Her diet had been unrestricted.

She still complained of weakness of the back and a burning lumbar backache after prolonged standing but was able to walk six to eight blocks without fatigue. Scant menstrual bleeding had occurred from July 22 to July 29 for the first time in four years. Physical examination showed no changes except that the facial acne and hirsutism had decreased. Roentgen examination of the thoracic and lumbar portions of the spine showed evidence of healing of the vertebral fractures, but marked demineralization of the skull and spine was still noted and had not improved since the examination made in April 1942. Estimations of the serum protein, phosphatase, calcium and phosphorus yielded values within the normal range. Serum cholesterol was found for the first time to be within the normal range (189 mg. per hundred cubic centimeters). A test of dextrose tolerance by the one hour, two dose method of Exton and Rose gave the following values: fasting blood sugar, 110 mg. per hundred cubic centimeters; one-half hour blood sugar, 146, and one hour blood sugar, 150. Urine collected during the test period contained no sugar. It is thus evident that some general improvement had occurred.

The testosterone propionate was supplied by the Schering Corporation. Part of the calciferol was supplied by the Winthrop Chemical Company.

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COLD HEMAGGLUTINATION WITH SYMMETRIC GANGRENE OF THE TIPS OF THE EXTREMITIES

REPORT OF A CASE

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The antigen-antibody reaction between human erythrocytes and serum in which hemagglutination is observed only at low temperatures (below 20 C.) has attracted the attention of immunologists [1] and clinicians [2] for many years. Unusual serologic features of this reaction, its association with so many diverse pathologic states (Raynaud's syndrome, acute and chronic acquired hemolytic anemias, trypanosomiasis, acute bacterial infections, cirrhosis of the liver, leukemia, pernicious anemia, lymphoblastomas and bland venous thrombosis [2a]) and its presence in low titer in at least 95 per cent of normal persons [3] have been recorded. There is only 1 report [4] of the occurrence of gangrene of the extremities due to the action of a cold hemagglutinin. In the case we are reporting gangrene was much more extensive.

In the data that follow the essential characteristics of the phenomenon are presented. The differences between cold hemagglutination, panagglutination and pseudoagglutination (rouleau formation) will not be discussed. Wiener [5] and Levine [6] have written exhaustively on this subject. The term autoagglutination will not be used, since it refers only to the agglutination of erythrocytes by

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From the Medical Service of Harlem Hospital, City of New York Department of Hospitals, Dr. Oswald La Rotonda, director, and the Littauer Pneumonia Research Fund of New York University College of Medicine, Dr. Jesse G. M. Bullowa in charge.

1. Landsteiner, K.: Ueber Beziehungen zwischen dem Blutserum und den Körperzellen, München. med. Wchnschr. **50**:1812, 1903.

2. Klein, A.: Ueber die Untersuchung der Formelemente des Blutes und ihre Bedeutung für die praktische Medizin, Wien. klin. Wchnschr. **40**:1569, 1890.

2a. Since this article was presented, two publications have appeared concerning the presence of cold hemagglutinins in atypical (virus?) pneumonia. They are as follows: Peterson, O. L.; Ham, T. H., and Finland, M.: Cold Agglutinins (Autohemagglutinins) in Primary Atypical Pneumonias, Science **97**:167, 1943. Horstmann, D. H., and Tatlock, H.: Cold Agglutinins: A Diagnostic Aid in Certain Types of Primary Pneumonia, J. A. M. A. **122**:369 (June 5) 1943.

3. Kettel, K.: Studien über die Frage der Kälteagglutination des Blutes bei Menschen; Vorläufige Mitteilung, Acta path. et microbiol. Scandinav. **5**:306, 1928.

4. McCombs, R. P., and McElroy, J. S.: Reversible Autohemagglutination with Peripheral Vascular Symptoms, Arch. Int. Med. **59**:107 (Jan.) 1937.

5. Wiener, A. S.: Blood Groups and Blood Transfusion, ed. 3, Springfield, Ill., Charles C Thomas, Publisher, 1943.

6. Levine, P.: On Pseudo-Agglutination and Cold Agglutination, Ukrain. Ztschr. f. Blutgruppenforsch. **2**:17, 1928.

homologous serum. It does not necessarily imply the all-important factor of cold. Cold hemagglutinins agglutinate homologous erythrocytes but in addition agglutinate all human and many animal erythrocytes.

REPORT OF CASE

The patient was a 64 year old American Negro who had lived in Virginia until his forty-fifth year, working in tobacco warehouses. He then moved to New York city. For the next five years he worked in an aluminum refinery. Here he was exposed to intense heat in close proximity to molten aluminum. On several occasions he sustained minor burns of the skin when the metal splashed. Toward the termination of this employment he noted the beginning of the disease which brought him under our observation fifteen years later.

He had had a penile sore in his youth but had never received antisyphilitic treatment. He was married at the age of 20. His wife had six pregnancies, all of which terminated in living children, none of whom have shown clinical or serologic evidence of syphilis.

Except for the present illness he had been remarkably well. Fifteen years before admission he noticed tingling, burning and numbness of the tips of his fingers and of his toes on exposure to a low environmental temperature. These symptoms invariably followed even a ten to fifteen minute exposure to the winter temperatures in New York. The symptoms started while the patient was in the cold; they rapidly subsided when he entered a warm room. Often he experienced sharp pain in the epigastrium accompanying the painful sensations in the extremities. This was also short lived, clearing up rapidly when the environmental temperature was raised. The first urine passed after any such episode was extremely dark, resembling coffee. There was no dysuria, however. Thereafter the urine looked normal to the patient. These attacks of pain in the abdomen and extremities and the dark urine occurred only and always after exposure to cold and except for transient distress did not inconvenience the patient. He looked on them as a "peculiar" reaction. Tingling or pain on exposure to cold was never experienced in the tip of the nose or lobes of the ears. He had never observed any tingling of the tongue or other uncomfortable sensations in his mouth or pharynx after the ingestion of cold drinks or ice cream. He had never experienced cyanosis or pallor of his digits, nor had he ever noted urticarial or other cutaneous reactions to cold.

Two weeks prior to admission to the Harlem Hospital, the patient was exposed to a dry early morning temperature of approximately 5 F. for about sixty minutes while waiting for a bus. During this time he was clad warmly and wore kid gloves and shoes and cotton socks. He was not able to exercise much during his long wait and spent most of the hour standing still. He observed the same tingling of his fingers and toes that he had experienced many times before, and the first urine passed was dark. On this occasion, however, though the urine shortly resumed its normal appearance, the tingling and the pain continued. These symptoms persisted with moderate severity, unrelieved by environmental warmth. Despite this discomfort he did not remain in bed but continued to be up and about indoors until the pain became so severe that he sought hospital care.

On his admission to the service of Dr. Oswald La Rotonda, on Jan. 17, 1942, he presented an unusual diagnostic problem. The general physical examination revealed an acutely ill, slightly obese, intelligent, darkly pigmented Negro. The rectal temperature was 102 F. Examination of the head and neck gave no significant results. Examination of the fundi revealed slight widening and irregularity of the arterial light reflex. The heart was of normal size. There were no abnormal sounds. The heart rate was regular, 90 beats per minute. The blood pressure was 160 systolic and 90 diastolic. The lungs were clear. The abdomen was obese. The viscera were not palpable, nor were there palpable masses. The results of neurologic examination were negative. In the upper extremities the arterial pulses were easily felt, from the subclavian to the digital. The axillary, radial, ulnar and digital arterial pulses had a bounding quality. Slight thickening of the radial arteries was evident on palpation. The tips of all the fingers to the distal interphalangeal joints were tense, tender, painful and cool to the touch. In the lower extremities all the arterial pulses were easily felt. These included the iliac, femoral, popliteal, anterior and posterior tibial and dorsal of the foot (the last three after subsidence of the edema). There were pitting tender edema and inflammatory warmth of each leg in the lower half anteriorly and the lower two thirds posteriorly. Both feet were moderately edematous and tender. The patient could not move his toes, and they were insensitive to pain stimuli. The toes were exquisitely tender and cool to the touch.

Detailed laboratory study gave the following results:

1. The specific gravity of the urine was 1.026 and the color amber; the urine was clear, and tests for albumin and sugar gave negative results; microscopic examination showed a rare white blood cell; the result of a benzidine test for occult blood was negative.

2. The Kahn test of the blood for syphilis gave negative results.

3. The roentgenologic examination of the chest revealed slight enlargement of the left ventricle; the lungs were normal.

4. The electrocardiogram revealed a depressed T_1 and a flat T_3 wave and left ventricular preponderance, changes indicative of myocardial disease.

5. Studies of the hepatic function revealed that the icterus index (acetone) was 3.0; the blood content of cholesterol, 180 mg., and of cholesterol esters, 90 mg. per hundred cubic centimeters; the reaction to the cephalin flocculation and the Takata-Ara test, negative;

Fig. 1.—Dry gangrene of the tips of the fingers.

the reaction to the galactose tolerance test, 2 Gm. excreted in four hours, and to the bromsulphalein excretion test (5 mg. per kilogram), less than 5 per cent dye retention in one-half hour; the blood content of albumin, 4.5 Gm., and of globulin, 2.5 Gm. per hundred cubic centimeters, and the serum formaldehyde-gel reaction, negative.

6. A test of renal function revealed a maximal specific gravity of the urine of 1.028; other determinations were not deemed necessary.

7. Roentgenologic examination of the gastrointestinal tract with special reference to the small intestine revealed hypermotility, puddling of barium sulfate, a segmental arrangement and loss of normal jejunal and ileal markings; when this procedure was repeated after three weeks of intensive treatment with thiamine hydrochloride (525 mg. given subcutaneously) the changes were less marked.

8. Roentgenologic examination of the arms, forearms, thighs and legs did not reveal any calcification of vessels.

When the patient was admitted a definite diagnosis was not made and the following tentative diagnoses were entertained: impending gangrene, thrombophlebitis or thromboangiitis obliterans and paroxysmal hemoglobinuria.

During the first week the patient was treated for thrombophlebitis; he continued to complain of pain in his toes and to a lesser degree in his fingers. His temperature remained between 101 and 102 F. The edema and pain in the legs gradually subsided. At the end of this period, despite his intense pigmentation, it became obvious that gangrene of all the toes and of the tips of seven fingers was taking place. In an attempt to delay or forestall some of these changes, he was treated with heparin and 3,3'-methylenebis-(4-hydroxycoumarin) for three weeks. No beneficial effect could be observed as a result of this medication.

At this time, one week after the patient's admission to the hospital, a chance observation provided the lead to the diagnosis. During the course of a hematologic study (of blood from the ear), almost complete agglutination of the red cells was visible grossly as soon as dilution in a counting pipet was carried out. After several efforts, a successful dilution was

Fig. 2.—Dry gangrene of the toes.

made with warm isotonic solution of sodium citrate, but when an attempt was made to perform the count several minutes later, clumping had again occurred. When this pipet with its contained cells and fluid was heated gently, complete dispersion of the cell clumps occurred.

The patient remained in bed for two months. During this time the temperature fell to normal and the progressive changes of dry gangrene of the digits developed.

The gangrene occupied all of the toes as far as the metatarsophalangeal joints. The fingers were much less severely involved. On the left hand the tips of the terminal phalanges of the second, third, fourth and fifth fingers were involved, whereas on the right both the first and second fingers were spared. This difference in degree was also demonstrated by roentgenographic means. Roentgenograms of the feet revealed several large, sharp, moth-eaten foci of bone destruction without any reaction in the proximal parts of the distal phalanges. There was no calcification in the blood vessels of the feet.

The pain gradually disappeared as the acute inflammatory element of the initial stages subsided. It could then be observed that the line of demarcation between the gangrene and

the normal skin was exceedingly sharp. During the next four months the patient was up in a wheel chair. Therapy to the lesions consisted of daily bathing of the feet in diluted solution of sodium hypochlorite U. S. P. and application of hydrous wool fat to the skin. Thymol iodide powder was dusted on the toes. The toes and the gangrenous foci of the fingers became sclerotic and mummified. Occasionally small purulent foci formed, but these drained spontaneously. Examination eleven months after the onset showed that all the gangrenous areas had sloughed and the stumps of the digits were healing. Figures 1 and 2 show the condition of the hands and feet two months after the onset of the gangrene.

The finding of hemagglutination in the red cell counting pipet provided the impetus for a detailed study of the characteristics of the phenomenon. Additional aspects of the problem will be presented in other communications.

EXPERIMENTAL STUDIES

1. *Characteristics of Cold Hemagglutination.*—The following experiments were performed:

(*a*) Venous blood was collected in a tube containing 3.8 per cent solution of sodium citrate and in a dry tube. The latter tube was placed at 37 C. and the blood allowed to clot firmly. The expressed clear serum was removed. The former tube was centrifuged; the plasma was removed and replaced with five volumes of 0.85 per cent sodium chloride solution. The mixture was warmed to 37 C. in a water bath and then centrifuged. This procedure of washing with warm saline solution and discarding the supernatant clear saline solution after centrifugation was performed six times. When red blood cells prepared in this manner were mixed with 0.85 per cent sodium chloride solution or normal human serum of the same blood group and kept at 4 or at 37 C. for one hour, they remained evenly dispersed (except for slight sedimentation) and agglutination did not occur. When the patient's serum, prepared as before, was mixed with either homologous or heterologous red blood cells and the mixture placed at 4 and at 37 C. for one hour, the most intense agglutination was observed in all instances at 4 C. but none at 37 C. (except low titer isoagglutination with red cells of other blood groups).

These experiments show that the agglutinating effect resided in the patient's serum and not in his red cells and that heterologous as well as homologous erythrocytes were agglutinated by it. The patient's red blood cells were not affected by heterologous human serum.

In all subsequent experiments the cells and serum of the patient were prepared in the manner described.

(*b*) A titration for agglutination at 4 C. was carried out. The erythrocytes were used in 2 per cent suspension. Mixtures of 0.1 cc. of a suspension of homologous red blood cells and 0.4 cc. of progressive geometric dilutions of the patient's serum were kept at 4 C. for sixteen hours, and agglutination was determined by gross and microscopic observation. This test was performed on many occasions, and fluctuation in titer was observed from 1:3,000 to 1:32,000; i. e., it was possible to show agglutination in the cold with a specimen of the patient's serum diluted 1:32,000 with 0.85 per cent sodium chloride solution. Retesting eleven months after the onset of the gangrene revealed the same titer of the serum. A serum wtih such extraordinary powers of cold agglutination has rarely been recorded. High titers of cold hemagglutination have been reported.[7] Cold hemagglutinins could not be demonstrated in the spinal fluid.[8]

(*c*) An understanding of the rapidity and the completeness of the cold agglutination reaction is essential to interpretation of the clinical observations in the present case. In an experiment to reveal these, 1 cc. of washed packed homologous red blood cells was mixed at room temperature with 1 cc. of the patient's serum. At this temperature the cells were slightly agglutinated. When the temperature was lowered to 4 C. by immersion of the tube in ice water, agglutination was grossly visible in less than one minute. In two minutes the

7. Wheeler, K. M.; Gallagher, H. J., and Stuart, C. A.: An Unusual Case of Auto-agglutination, J. Lab. & Clin. Med. **24**:1135, 1939. Jessen, C. U., and Bing, J.: Methods for Differentiating the Cause of Increased Sedimentation Rate, Acta med. Scandinav. **105**: 287, 1940.

8. Riebeling, C.: Ueber einen Fall von sog. Panagglutination, Med. Klin. **29**:1440, 1933.

cells were tightly agglutinated. The mass of agglutinated cells had the appearance of a gel. When the temperature was changed to 37 C. by immersion in a constant temperature water bath, breaking up of the massive agglutination was apparent in thirty seconds, and in two minutes complete dispersion of the red blood cells had occurred. If the temperature was suddenly lowered to 4 C. the same rapid agglutination occurred. This process could be repeated many times without apparent cellular injury or change in the phenomenon.

(*d*) Experiments were performed to show more clearly the relationship of agglutination to temperature. Geometric dilutions of the patient's serum were incubated for one hour with the patient's red blood cells, as in experiment *b*, at various temperatures and agglutination recorded. The results of this experiment are shown in the following tabulation:

Temperature (C.)	Agglutination Titer
0	+ 1:3,200
4	± 1:3,200
6	+ 1:1,600
13	+ 1:800
20	± 1:50
28	Negative

(*e*) An experiment to demonstrate the action of the antibody in vivo was carried out. Iwai and Meisai [9] described visible agglutination of the red blood cells in the conjunctival capillaries of 2 patients with Raynaud's syndrome and a high titer (1:500 to 1:1,000) of cold hemagglutination. Other studies have demonstrated erythrocyte agglutination in postmortem tissue sections.[10]

The venules and capillaries of the bulbar and palpebral conjunctivas in each eye were visualized under the slit lamp binocular corneal microscope and were seen to be normal. The conjunctival sacs were irrigated with 100 cc. of iced isotonic solution of sodium chloride for one and one-half minutes and the vessels immediately observed. A picture was seen similar to that of the retinal vessels in the early postagonal state. Marked segmentation of the blood columns—apparently by clumps of erythrocytes—was readily seen. Between neighboring clumps one could see what appeared to be clear plasma. The segments and clumps were moving slowly. As observation was continued and the eye exposed to a normal environmental temperature (24 C.), the segmentation slowly disappeared. This procedure was carried out several times in each eye without complications. The distress of the intense cold was soon dissipated. Irrigation of the conjunctival sacs of a normal person in this manner gave rise to an immediate blanching, followed by a reactive hyperemia.[11] Figure 3 demonstrates the effect of cold on the conjunctival vessels of the patient's eye.

2. *Hemoglobinuria.*—The reliable history of the repeated passage of coffee-colored urine after exposure to cold and the absence of hemoglobin in routine urinalyses made study of this point important. It had been shown by other investigators that in syphilitic cold hemoglobinuria (presence of a cold hemolysin and a positive Donath-Landsteiner reaction [12]) immersion of an extremity in cold water was often followed by a paroxysm of hemoglobinuria (Rosenbach [13]). The following experiment was carried out in an attempt to demonstrate hemolysis in vivo in the present instance:

The syringes were adequately rinsed in 0.85 per cent sodium chloride solution, and 9 cc. of venous blood was drawn carefully without undue stasis from each arm into 1 cc. of freshly prepared 3.8 per cent sodium citrate solution. The blood and the anticoagulant were gently mixed. The right forearm was then immersed in a basin of cracked ice and water (temperature 4 C.) for twenty-five minutes and the left arm kept at room temperature (20 C.). After ten minutes had elapsed venous blood, as before, was drawn from the left arm. At the end of twenty-five minutes the right arm was removed from the water and dried, and

9. Iwai, S., and Meisai, N.: Etiology of Raynaud's Disease, Japan M. World **6**:345, 1926.
10. Lewin, O.: Zur Frage der Zulässigkeit der Bluttransfusion bei bestehender Panagglutination, Wien. klin. Wchnschr. **47**:714, 1934.
11. Irrigation was performed with the assistance of Dr. Arthur Minsky, associate ophthalmologist, Harlem Hospital.
12. Hemolysis after warming of chilled blood.
13. Rosenbach, cited by MacKenzie, G. M.: Paroxysmal Hemoglobinuria: Review, Medicine **8**:159, 1929.

then venous blood was drawn from each arm. Both arms remained at room temperature. At appropriate intervals for one and a half hours blood was drawn from the two arms simultaneously. All samples were then centrifuged and the supernatant plasma removed. The various specimens of plasma obtained were tested for hemoglobin by a quantitative technic which was a modification of the benzidine method of Bing and Baker.[14] Urine was obtained before and after the experiment and tested for the presence of hemoglobin. Two samples of the plasma from the arm which had been in the cold were analyzed in the Hardy recording spectrophotometer[15] for determination of the nature of the pigments present. The results of these studies are shown in figures 4 and 5.

Hemolysis occurred only in the cold extremity, showing that it was a local phenomenon. The pigment liberated to the plasma was oxyhemoglobin, indicating that chemical change

Fig. 3.—Bulbar conjunctiva immediately after irrigation of the conjunctival sac with cold saline solution. Below are the cornea and iris. Note the blood vessels and the segmental interruption of the blood column in the left third of the vessel running transversely (× 25).

did not occur, for this is the normal pigment of the red blood cells. Note should be taken of the rapidity with which the hemoglobin disappeared from the plasma. The lack of hemoglobinemia in the warm arm and the absence of hemoglobinuria may be explained by several factors. The cold undoubtedly caused marked reduction in the blood flow in the exposed arm; the free hemoglobin was rapidly diluted with the plasma of the remainder of the body; the mechanisms which existed for the removal of plasma hemoglobin rapidly removed this

14. Bing, F. C., and Baker, R. W.: Purification of Benzidine, and an Improved Reagent for Estimating Hemoglobin, J. Biol. Chem. **95**:387, 1932.

15. The analysis was performed at the Electrical Testing Laboratories, Inc., New York.

pigment. There were no untoward symptoms in the patient as a result of this or similar experiments. There was no systemic or local reaction. Undue hemolysis intra vitam was not observed in other experiments as a consequence of prolonged venous stasis.

3. *Syphilis.*—The exclusion or inclusion of syphilis as a contributing factor was deemed essential because of the history that a chancre had probably once been present, that coffee-colored urine had been passed after exposure to cold and that an antibody acting in the cold against homologous red blood cells was present.

a. The reactions to serologic tests[16] were as follows: diagnostic Kahn test of the blood, negative heavy; Kahn exclusion test of the blood, ±; Wassermann test of the blood, negative; Mazzini test of the blood, 2 plus; Kahn verification test of the blood, negative type; Wassermann test of the spinal fluid, negative; Kahn test of the spinal fluid, negative, and colloidal gold curve test of the spinal fluid, 0000000000.

b. The Donath-Landsteiner test[12] was performed many times with varying serologic technics. The erythrocytes were used in concentrations of 30, 20, 10 and 5 per cent packed volume. The patient's serum was used fresh or inactivated (by heat) with the addition of an excess of active guinea pig complement. The period for cold incubation varied from ten minutes to one hour. In none of these tests was a positive result obtained. All tubes containing the patient's serum and cells showed agglutination in the cold.

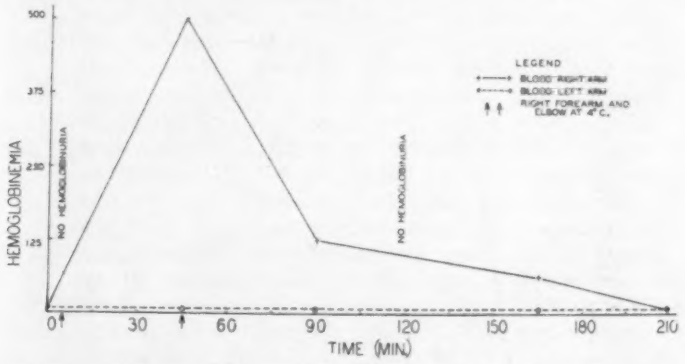

Fig. 4.—The relationship between hemoglobinemia and the time after exposure of the forearm to cold. The hemoglobinemia is expressed in milligrams of hemoglobin per hundred cubic centimeters of plasma.

We conclude from these serologic tests and from the absence of clinical evidence of syphilis that the patient had no evidence of active syphilitic infection.

4. *Hematologic Status.*—The rare occurrence of cold hemagglutination associated with hemolytic anemia, the history of passage of coffee-colored urine and the occurrence of hemoglobinemia on exposure to cold made the determination of the status of the blood important.

Studies of the blood showed the following picture:

Hemoglobin, 84 per cent (14.5 Gm. per hundred cubic centimeters = 100 per cent)
Red cells, could not be counted accurately
White cells, 12,000 per cubic millimeter
Platelets, could not be counted accurately
Segmented neutrophils, 56 per cent
Nonsegmented neutrophils, 4 per cent
Lymphocytes, 31 per cent

16. The Kahn tests were performed by Dr. Reuben Kahn, Ann Arbor, Mich.

Monocytes, 6 per cent
Segmented eosinophils, 3 per cent
Reticulocytes, 1.5 per cent
Hematocrit reading, 39.1 per cent
Hypotonic fragility of red cells: no hemolysis, 0.72 to 0.48 per cent sodium chloride solution; partial hemolysis, 0.44 to 0.36 per cent sodium chloride solution; complete hemolysis, 0.32 per cent sodium chloride solution
Price-Jones curve: diameters of red cells (500), 7.30 microns; curve of all diameters, normal
Quantitative test of urobilinogen excretion (Watson's method [17]): stool (four days), 70.2 mg. per day; urine (two days), 0.8 mg. per day
Bleeding time (Duke's method), three minutes
Coagulation time (Lee and White method), eleven minutes
Clot retraction, present in four hours

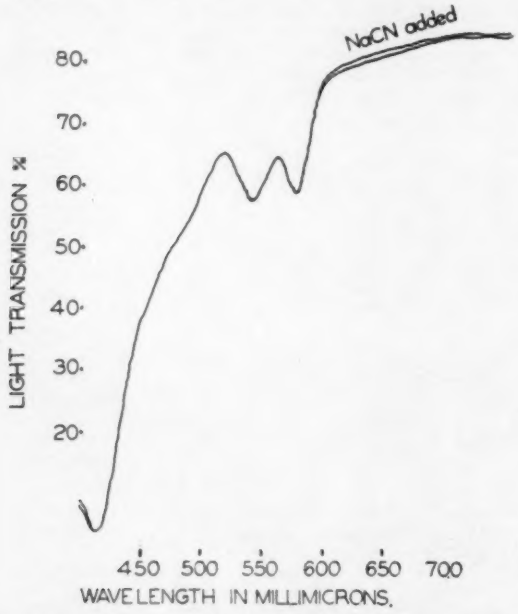

Fig. 5.—Spectrophotometric analysis of the hemoglobin pigment liberated, as shown in figure 4.

Sedimentation rate (Wintrobe's method): one hour—at 1 C., 4.5 mm.; at 9 C., 22.0 mm.; at 19 C., 29.0 mm.; at 24 C., 15.5 mm.; at 37 C., 48.5 mm.
Plasma prothrombin index (Quick's method), 100 per cent
Blood group O; Rh factor absent; MN type; anti-Rh antibody absent
Serum isoagglutinin titer: anti-A, 1/128; anti-B, 1/32
Hemolysis test with acidified serum (used by Ham [18] in cases of paroxysmal nocturnal hemoglobinuria), negative result

From these figures we conclude that there was no significant abnormality in the peripheral blood and that the rate of destruction of erythrocytes was normal.

17. Watson, C. J.: Concerning Urobilinogen: An Improved Method for the Approximate Quantitative Estimation of Urobilinogen in Urine and Feces, Am. J. Clin. Path. **6**:458, 1936.
18. Ham, T. H.: Studies on Destruction of Red Blood Cells: Chronic Hemolytic Anemia with Paroxysmal Nocturnal Hemoglobinuria; Investigation of Mechanism of Hemolysis with Observations on Five Cases, Arch. Int. Med. **64**:1271 (Dec.) 1939.

COMMENT

The serologic studies reported afford a rational explanation of the patient's illness. It seems reasonable to suggest a similarity of the action of the cold hemagglutinin intra vitam to that observed in vitro. This is shown by the observation of erythrocyte agglutination in the capillaries of the conjunctiva after this was cooled. It is to be expected, then, that marked cooling of the body in any portion will be followed by hemagglutination. Both the in vivo and the in vitro experiments indicated the rapidity of this reaction at a low temperature and its prompt disappearance as the temperature rose. The episodes of tingling of the hands and feet that the patient noticed on exposure to cold can reasonably be explained on this basis.

The fact that the patient never experienced symptoms of vascular insufficiency in the lobes of the ears or tip of the nose at low temperatures or in the tongue or pharynx after ingestion of a cold drink cannot be explained. Some patients described in the literature as having a cold agglutination titer lower than our patient's presented such symptoms. The localization of the symptoms to the fingers and toes is in part explained by a normal large temperature gradient in these parts. A fall in temperature in the fingers and toes on exposure of the entire body to cold is a normal phenomenon.[19] It should be emphasized that we were not able to find any evidence of organic vascular disease, such as arteriosclerosis or thromboangiitis obliterans. Many patients with a relatively high titer of cold hemagglutination never have symptoms of arterial insufficiency.

The last attack, the one resulting in acrogangrene, was apparently similar to the previous ones, differing quantitatively in that the cold was more severe and persisted for a longer period. It would appear that at this time the intense agglutination occluded many small peripheral blood vessels interfering with, or stopping, the blood flow. The period of vascular insufficiency was so prolonged that organic ischemic changes occurred in the vessels and the tissues of these regions. Capillary thrombosis was the probable result. Finally, even with rewarming of the part, when the agglutination should have broken up, reestablishment of the circulation could not be effected and dry gangrene resulted. That such a phenomenon might occur was predicted by Amzel and Hirszfeld.[20]

There are numerous other conditions in which episodes of arterial insufficiency of the extremities occur despite the absence of disease of the larger arteries. In severe anemia the oxygen-carrying capacity of the blood is so reduced as to give rise to tingling and other sensations. Similar symptoms are common in polycythemia vera, in which the viscosity of the blood may play an important role. A report [21] of the occurrence of Raynaud's syndrome in association with multiple myeloma with hyperglobulinemia indicates that intense rouleau formation may at times interfere with circulation. Cases reported as instances of chronic acroasphyxia have been characterized by long-standing coldness and cyanosis of the fingers and toes which might progress to gangrene. A recently observed case [22] of marked mitral stenosis with superimposed acute bacterial endocarditis was characterized by coldness and cyanosis of the digits. Similar phenomena [23] have been observed in cases of ball valve thrombi of the left auricle associated with

19. Lewis, T.: Observations on Some Normal and Injurious Effects of Cold upon the Skin and Underlying Tissues, Brit. M. J. **2**:795, 1941.

20. Amzel, R., and Hirszfeld, L.: Ueber die Kälteagglutination der roten Blutkörperchen, Ztschr. f. Immunitätsforch. u. exper. Therap. **43**:526, 1925.

21. Wintrobe, M. M., and Buell, M. V.: Hyperproteinemia Associated with Multiple Myeloma, Bull. Johns Hopkins Hosp. **52**:156, 1933.

22. Personal observation of the authors.

23. Fishberg, A. M.: Heart Failure, Philadelphia, Lea & Febiger, 1940.

mitral stenosis. In such cases the arterial insufficiency of the extremities is due to obstruction of the circulation at the mitral orifice. "Epinephrine shock," with marked coldness, pallor and cyanosis of the extremities, has been described as a manifestation of severe prolonged crises in cases of pheochromocytoma of the adrenal medulla.[24] In shock, or circulatory collapse due to severe injury from burns or other causes, insufficiency of the peripheral circulation is due to pooling of the blood in the splanchnic area. Finally, there is that group of conditions classified as Raynaud's syndrome, in which a vasomotor disturbance may be responsible for the ischemia.[25]

The occurrence of dry gangrene of the digits in the presence of normal pulsations of the larger arterial vessels is rare. Case 2 of Nygaard and Brown [26] is one of gangrene of the toes of undetermined cause, though the authors demonstrated an abnormality in the coagulation of the blood. Lewis [27] discussed this syndrome, mentioning the unusual appearance of gangrene in syphilitic paroxysmal hemoglobinuria, in which functional vasomotor phenomena are common. Under the heading of "Bilateral Gangrene of the Digits in the Young and in the Elderly" he mentioned the relationship to acute infections, wasting diseases and Raynaud's syndrome. He did not include cold hemagglutination as a cause of symmetric gangrene. Symmetric gangrene associated with widespread purpura was reported by Fatheree and Hines.[28] Symmetric gangrene due to vasospasm is a common occurrence in epidemics of ergotism.[29] Similar gangrene has been reported as following the use of ergotamine tartrate for the relief of pruritis.[30] We are omitting from this discussion the effect of physical agents as a cause of gangrene. A review of all the published cases of cold hemagglutination reveals 12 instances of functional vasomotor disturbances of the extremities [31] and 1 instance of gangrene.[4] In our case gangrene was more extensive than in the one previously reported.

Though we were never able to reproduce the hemoglobinuria, we have no doubt that it occurred many times, as stated by the patient. The result of the in vivo

24. Engel, F. L.; Mencher, W. H., and Engel, G. L.: "Epinephrine Shock" as a Manifestation of a Pheochromocytoma of the Adrenal Medulla, Am. J. M. Sc. **204**:649, 1942.

25. Hunt, J. H.: Raynaud Phenomena: Critical Review, Quart. J. Med. **5**:399, 1936.

26. Nygaard, K. K., and Brown, G. E.: Essential Thrombophilia, Arch. Int. Med. **59**:82 (Jan.) 1937.

27. Lewis, T.: Vascular Disorders of the Limbs Described for Practitioners and Students, New York, The Macmillan Company, 1936.

28. Fatheree, T. J., and Hines, E. A., Jr.: Symmetrical Gangrene of Extremities Associated with Purpura, Am. Heart J. **12**:235, 1936.

29. Barger, G.: Ergot and Ergotism, London, Gurney & Jackson, 1931.

30. Yater, W., and Cahill, J. A.: Bilateral Gangrene of the Feet Due to Ergotamine Tartrate Used for Pruritis of Jaundice, J. A. M. A. **106**:1625 (May 9) 1936.

31. (*a*) Iwai, S., and Meisai, N.: Etiology of Raynaud's Disease, Japan M. World **5**:119, 1925. (*b*) Alexander, H. L., and Thompson, L. D.: Autohemagglutination in Chronic Leukemia, J. A. M. A. **85**:1707 (Nov. 28) 1925. (*c*) Iwai and Meisai.[9] (*d*) Stieffel, R.: Etude des hémoglobinuries, Thesis, Paris, Louis Arnette, 1928. (*e*) Davidson, L. S. P.: Macrocytic Haemolytic Anemia, Quart. J. Med. **1**:543, 1932. (*f*) Roth, G.: Paroxysmal Hemoglobinuria with Vasomotor and Agglutinative Features, Proc. Staff Meet., Mayo Clin. **10**:609, 1935. (*g*) Salén, E. B.: Thermostabiles nicht komplexes (Auto-) Hämolysin bei transitorischer Kälthämoglobinurie, Acta med. Scandinav. **85**:570, 1935. (*h*) Hanns, A., and Sommer, A.: Acrocyanose, auto-agglutination des hématies, hémoglobinurie paroxystique, Strasbourg méd. **98**: 172, 1938. (*i*) Gautier, C.; Heimann, V., and Laudat, M.: Grande auto-agglutination des hématies. Lymphome splénique. Crises de cyanose. Action remarquable de la radiothérapie sur le déséquilibre des albumines du sérum, Bull. et mém. Soc. méd. d. hôp. de Paris **55**:59, 1939. (*j*) Benians, T. H. C., and Feasby, W. R.: Raynaud's Syndrome with Spontaneous Cold Hemagglutination, Lancet **2**:479, 1941. (*k*) Sezary, A.; Kipfer, H., and Gharib, M.: "Livedo annularis" et crises de cyanose chez un sujet atteint de maladie hémolytique avec grande auto-agglutination des hématies, Bull. et mém. Soc. méd. d. hôp. de Paris **54**:1710, 1938.

experiment in which the arm was cooled indicates that marked hemoglobinemia occurred locally at the site of action of the agglutinin. When such a process was widespread, even if the hemoglobinemia in any one site was not so great as in the experiment, the probability of hemoglobinuria would be increased. In addition to the present case, hemoglobinuria in association with cold hemagglutination was reported in 17 cases.[32] It is not possible to say how often a pathogenetic relationship existed between the hemoglobinuria and the cold hemagglutination in these reported cases. Several were instances of acute hemolytic anemia. It is well known that hemoglobinuria in the absence of cold hemagglutination may occur in such states.

When a clearcut relationship between cold and hemoglobinuria can be shown, it is likely that the cause of the hemoglobinuria is in the activation of the cold hemagglutinin. However, when hemoglobinuria occurs at room temperature, or even at a higher temperature, there is good reason to doubt a close causal relationship between the hemoglobinuria and a cold hemagglutinin which may be present. In no case of hemolytic anemia with hemoglobinuria and cold hemagglutination has the close dependence of the hemoglobinuria on a fall in temperature been demonstrated. Some of the patients with hemolytic anemia due to a sulfonamide compound were febrile before or at the onset of the hemolytic process. There is a definite possibility that the phenomenon of cold hemagglutination in certain instances of hemolytic anemia may be unrelated to the mechanism of hemoglobinuria.

Besides the fact that hemoglobinuria may occur in the absence of cold hemagglutination is the knowledge that there are numerous examples of cold hemagglutinins of high titers without hemoglobinuria.

SUMMARY AND CONCLUSIONS

A case of symmetric gangrene of the tips of the extremities due to cold hemagglutination is described.

Experimental studies revealed: (*a*) unilateral hemoglobinemia following exposure of a forearm to cold, (*b*) hemagglutination in the capillaries of the conjunctiva due to cold and (*c*) absence of syphilis or evidence of a hemolytic anemia. No cause could be found to explain the presence of the cold hemagglutinin.

A discussion is presented of clinical conditions in which transient or permanent arterial insufficiency of the extremities occurs despite adequate pulsation and absence of disease of the peripheral arteries.

All the cases of cold hemagglutination reported in the literature in association with arterial insufficiency of the extremities or hemoglobinuria are tabulated.

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32. (*a*) Mino, P.: Einiges über Konstitutionslehre und serologische Forschung, Deutsche med. Wchnschr. **50**:1533, 1924. (*b*) Köpplin, F.: Autohämagglutination und Anämie, Ztschr. f. klin. Med. **130**:784, 1936. (*c*) Watson, C. J.: Hemolytic Jaundice and Macrocytic Hemolytic Anemia, Ann. Int. Med. **12**:1782, 1939. (*d*) Antopol, W.; Applebaum, I., and Goldman, L.: Two Cases of Acute Hemolytic Anemia with Auto-Agglutination Following Sulfanilamide Therapy, J. A. M. A. **113**:488 (Aug. 5) 1939. (*e*) Reisner, E. H., and Kalkstein, M.: Auto-Hemolysinic Anemia with Autoagglutination: Improvement After Splenectomy, Am. J. M. Sc. **203**:313, 1942. (*f*) Rothstein, I., and Cohn, S.: Acute Hemolytic Anemia, Autoagglutination, Toxic Hepatitis and Renal Damage Following Sulfathiazole Therapy, Ann. Int. Med. **16**:152, 1942. (*g*) Dameshek, W.: Cold Hemagglutinins in Acute Hemolytic Reactions Following Sulfonamide Medication and Infection, J. A. M. A. **123**:77 (Sept. 11) 1943. (*h*) McCombs and McElroy.[4] (*i*) Alexander and Thompson.[31b] (*j*) Stieffel.[31d] (*k*) Roth.[31f] (*l*) Salén.[31g] (*m*) Hanns and Sommer.[31h]

Progress in Internal Medicine

VASCULAR DISEASES

NINTH ANNUAL REVIEW

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REVIEW OF SOME OF THE RECENT LITERATURE

The present review was obviously compiled under wartime conditions, and many articles have been omitted because the journals were not available for study. These are known to us and will be included in future reviews. Although there has not been a noticeable decline in original material during the past year, it is anticipated that such a condition will prevail as more and more investigators enter military service or attend to their busy wartime practices. Dicoumarin (3,3'-methylene-bis-[4-hydroxycoumarin]) has been given considerable attention in this review, and the many articles on heparin have been omitted pending decision as to their value when this drug is finally compared with the former compound.

PHYSIOLOGY

The causative factor responsible for pain in an ischemic extremity has been subject to considerable controversy. Harpruder and Stein [1] report their observations on the genesis of ischemic pain, substantiating in part the theory of the so-called P substance as the responsible agent. Their studies were done in the usual manner. Pain was produced by movements of the fingers of an arm made ischemic by a blood pressure cuff inflated to 200 mg. of mercury. Before the cuff was inflated an average of forty contractions of the fingers was possible before pain developed. After the cuff was inflated and the arm rendered ischemic, only one-third to one-half the same number of contractions were possible. With this as a control experiment, other studies were performed as follows: It was first noted that pain could not be transferred from the lower to the upper extremities. This was demonstrated by producing an ischemic pain in the lower extremities, releasing the pressure and within forty seconds repeating the previously mentioned control experiment. No change in pain threshold was noted. The authors were next able to ascertain a phase of recovery; namely, three to five minutes could elapse between experiments and similar results be obtained. When the ischemic extremity was immersed in a water bath at a temperature of 115 F., pain rapidly developed, similar to that produced with exercise. Pain did not develop

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1. Harpruder, K., and Stein, I. D.: Studies on the Nature of Pain Arising from an Ischemic Limb: I. Clinico-Experimental Observations, Am. Heart J. **25**:429 (April) 1943.

when the arm was immersed in cold water. Since certain investigators have considered vasodilatation as a cause for pain in ischemia, the authors dilated the vessels of the upper extremities reflexly and then rendered one arm ischemic; they found little change from the pain threshold of the control experiment. Oxygen likewise had little influence on the pain, as no change could be elicited in patients artificially rendered anoxic. Of interest were the reflex secondary effects of exercising the ischemic extremity. Both the systolic and the diastolic pressure were greatly elevated after exercise, usually returning to normal after two minutes' rest.

In a second article [2] is a report of chemical studies performed on venous blood obtained before the experiment, when pain developed and after the recovery phase. Lactic acid increased with exercise and further increased during the recovery phase, which indicates that there is no relationship between the concentration of this substance and the pain. The concentrations of histamine, ammonia and epinephrine in the blood and the oxidation potential and the conductivity of serums were also determined, but no essential change was shown. Serum potassium was of particular interest, because it was found to be elevated only during the period of pain. When potassium was injected intra-arterially the pain was so intense that only a few subjects were submitted to this procedure. The authors concluded that potassium plays a major role in the genesis of ischemic pain, most likely by its liberation from the cells and rapid accumulation in sufficient concentration to stimulate the pain end organs in muscle.

Capillaries.—Eichna and Bordley [3] studied the digital capillary blood pressure in normal and in hypertensive subjects and found it to vary within wide limits but to be qualitatively and quantitatively similar in the two groups. Under such physiologic influences as neurogenic vasoconstriction, reactive hyperemia, reflex vasodilatation and variations in cutaneous temperature between 27 and 35 C. (80.6 and 95 F.), small changes in capillary pressure were noted but the resultant values did not fall beyond "resting" limits. Only during increases in local venous pressure did the digital capillary blood pressure consistently exceed "resting" values. Wide variations in digital capillary blood pressure persisted during reflex vasodilatation, a state during which digital circulation is considered to be full, standard and reproducible. During vasodilatation, induced either reflexly or by locally injected histamine, there was a disproportionately greater increase in pressure in the venous limb than elsewhere in the capillary. The other states all influence the digital capillary blood pressure equally in all portions of the capillary. No correlation existed between the digital capillary blood pressure and arterial pressure, except perhaps during the hyperemia induced by histamine. The similarity of the digital capillary blood pressure of normal and that of hypertensive subjects indicates that in the digits the increased vascular resistance of hypertensive subjects is precapillary, presumably arteriolar.

Eichna [4] also compared the digital capillary pressure in hypertension induced by paredrinol sulfate (α-N-dimethyl-*p*-hydroxyphenylthylamine sulfate) with normal arterial pressure. He found them to be essentially the same. This observation

2. Harpruder, K., and Stein, I. D.: Studies on the Nature of Pain Arising from an Ischemic Limb: II. Biochemical Studies, Am. Heart J. **25**:438 (April) 1943.

3. Eichna, L. W., and Bordley, J.: Capillary Blood Pressure in Man: Direct Measurements in the Digits of Normal and Hypertensive Subjects During Vasoconstriction and Vasodilatation Variously Induced, J. Clin. Investigation **21**:711 (Nov.) 1942.

4. Eichna, L. W.: Capillary Blood Pressure in Man: Direct Measurements in the Digits During Arterial Hypertension Induced by Paredrinol Sulfate, J. Clin. Investigation **21**:731 (Nov.) 1942.

was equally true for capillaries of digits with intact innervation and for those of persons who had undergone preganglionic sympathectomy. At the height of the paredrinol-induced hypertension, the vasodilatation of local hyperemia did not significantly alter the digital capillary blood pressure. The hyperemia of the histamine flare was usually associated with a rise in the digital capillary blood pressure to a value which just exceeded the pressure obtained during the resting state at both normal and elevated arterial pressures.

Neumann, Cohn and Burch have continued their studies on the reactions of the small vessels following application of sensory stimuli at distant parts of the body. Their methods for measuring the spontaneous variations in the volumes of fingers and toes have been described in previous reviews. In one recent study [5] they stress the importance of the conditions under which these experiments are to be undertaken, such as uniform temperature, humidity and state of digestion. These are well known to investigators in this field, but the authors show objective evidence to support the belief that the patient's mental comfort and the degree of his relaxation are equally important. This was demonstrated by converting a "laboratory" into a conventional bedroom and by observing how the frequency of reaction on the part of the peripheral vessels increased when sensory stimuli were applied. Studies were performed on persons under both types of environment. In many instances better reactions were obtained in the hypertensive or senile patients after a simple change in atmosphere. These subjects frequently had reactions similar to normal subjects because of their ability to relax in a more suitable atmosphere. The same authors, in a study reported in a second communication,[6] found the mean reaction times of the tips of the fingers of normal persons to be 3.12 seconds, of senile persons 3.86 seconds and of hypertensive subjects 2.94 seconds. For the tips of the toes of the same subjects the times were more prolonged, being 3.43, 4.25 and 3.24 seconds respectively, but the delay is of the same order of magnitude in each of the three groups when compared with the values for the fingers. The authors accounted for this difference on the basis of the time required for the efferent impulses to traverse the additional length of postganglionic sympathetic fibers in order to reach the toes. The reason for the differences in each group of patients could not be explained excepting on the basis of changes in the vessels themselves or of a factor outside the vessels, such as the nervous system or a chemical state which influences the vessels.

In a previous review the reactive hyperemia ring test of Di Palma and others was described. This procedure was used to measure the ability of the smallest blood vessels of the skin to respond to local ischemia followed by a reactive hyperemia. By noting the time required for the area of ischemia to clear, a direct indication of the rate of local flow is obtained. The time required for local ischemia is designated the threshold time, and that required for clearing, the clearing time. All measurements are recorded in seconds with a standard stopwatch. The test was later termed the capillary sensitivity test. In brief, it is a more scientific version of the older method of applying pressure to the skin with a finger and noting the time required for the ischemic imprint to fade to the color of the surrounding skin.

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5. Neumann, C.; Cohn, A. E., and Burch, G. E.: A Study of the Influence of the Character of an Examining Room on the Peripheral Blood Vessels of Normal, Hypertensive, and Senile Subjects, J. Clin. Investigation **21**:651 (Nov.) 1942.

6. Burch, G. E.; Cohn, A. E., and Neumann, C.: Reactivity of Intact Blood Vessels of the Fingers and Toes to Sensory Stimuli in Normal Resting Adults, in Patients with Hypertension, and in Senile Subjects, J. Clin. Investigation **21**:655 (Nov.) 1942.

In the first of a series of new articles Di Palma and Foster [7] note the segmental and aging variations of reactive hyperemia in human skins. The threshold and clearing times were ascertained in fourteen dorsal and fifteen ventral positions, covering all the cutaneous branches of nerve segments from the ophthalmic division of the fifth cranial nerve to the fifth sacral nerve. It was noted that the more caudal the nerve segment, the higher the threshold and clearing times. With advancing age similar results were obtained but the gradient was marked and practically limited to the lower extremities. In another article, Di Palma, Muss and Foster [8] compare their readings obtained by this test on 24 patients suffering from arteriosclerosis obliterans with the oscillometric index and the results of thermometric and histamine flare tests. As the ring test showed the state of the circulation in the superficial vessels, the investigators obviously were unable to correlate the readings secured in this test with those obtained with the oscillometer, but they were in agreement with those obtained with histamine. It was not unusual to obtain normal results in reactive hyperemia ring tests over the ankle and foot, considering the age of the patient, even in advanced stages of obliteration of arterial trunks. On the other hand, the test was useful from a prognostic standpoint, in that the results were directly proportional to the symptoms, they paralleled collateral circulation and the clearing time was greatly prolonged in gangrenous areas. The test appears to be another means for evaluating the function of the fine vessels of the skin.

In their studies reported in a third article Di Palma and Foster [9] were unable to demonstrate any differences in response between the small dermal vessels of normal persons and of patients with benign hypertension, with hypertension associated with arteriosclerosis, or with uncomplicated arteriosclerosis. On the other hand, of 11 patients with malignant hypertension 10 had a response of the small vessels which indicated greatly decreased sensitivity. Thirteen patients with hypertension complicated by neurologic disorders were found to have cutaneous vessels as much as eighteen times more sensitive than those of persons in the normal and the other hypertensive groups. The authors concluded that the humoral agent now believed responsible for arterial hypertension does not exert its influence on the smallest vessels in the benign stages of the disease but may do so in a later, malignant phase.

Di Palma [10] also noted the responsiveness of the smallest blood vessels of the human skin in systemic anoxemia, hypercapnia, acidosis and alkalosis. His observations demonstrated that systemic anoxemia causes a decrease in sensitivity to local ischemia and a slowing of blood flow, whereas hypercapnia is capable of preventing these changes. With systemic acidosis there are a decrease in sensitivity to local ischemia and a slowing of blood flow. The exact opposite takes place in systemic alkalosis. These changes usually occurred independently of changes in

7. Di Palma, J. R., and Foster, F. I.: The Segmental and Ageing Variations of Reactive Hyperemia in Human Skin, Am. Heart J. **24**:332 (Sept.) 1942.

8. Di Palma, J. R.; Muss, I., and Foster, F. I.: A Reactive Hyperemia Ring Test in the Study, Evaluation and Prognosis of Pedal Lesions Caused by Arteriosclerosis Obliterans and Arterial Embolism, Am. Heart J. **24**:345 (Sept.) 1942.

9. Di Palma, J. R., and Foster, F. I.: Sensitivity of Smallest Cutaneous Blood Vessels: Quantitative Responses to Graded Mechanical Stimulation and to Local Ischemia in Arterial Hypertension, Arteriosclerosis, and Certain Allied Disorders, J. Clin. Investigation **21**:675 (Nov.) 1942.

10. Di Palma, J. R.: Quantitative Alterations in the Hyperemia Responses to Local Ischemia of the Smallest Blood Vessels of the Human Skin Following Systemic Anoxemia, Hypercapnia, Acidosis, and Alkalosis, J. Exper. Med. **76**:401 (Nov.) 1942.

pulse rate, blood pressure and respiratory rate and depth. Di Palma advances the view that the carbon dioxide concentration in the blood, or something directly associated with it, is the most important factor determining the sensitivity of these vessels, rather than oxygen saturation or changes in p_H.

Hertzman and Roth [11] demonstrated the selective effects of local cold on the terminal pad vessels and the digital artery of the chilled finger by means of their photoelectric plethysmograph. The digital artery does not participate in the vasoconstrictor reflexes elicited by the cold, but it will ultimately constrict if cold is continued, owing to the direct effects of the fall in temperature on the artery. Reactive dilatation also takes place in the reverse order, as the digital artery will finally relax when the rise in temperature of the finger permits relaxation of this artery. In a few normal subjects the reactive dilatation produced a pad pulse similar to that seen in chronic hypertension. This suggested to the authors that one of the factors responsible for the change in pad pulse form in hypertension may be the shunting of blood through direct arteriovenous communications.

The same authors [12] performed a number of experiments to demonstrate the absence of vasoconstrictor reflexes in the forehead. They were unable to obtain spontaneous rhythmic constrictions of vasomotor origin over this area, even though they were readily obtained in the finger. Also lacking were the usual vasoconstrictor reflexes elicited by startle, awakening, a deep breath, immersion of the hand in ice water or local application of cold. The responses in the forehead resembled those in a sympathectomized digit. Constriction is gradual after cold is applied locally but appears to be due to the direct effects of cold on the vessels. In addition, the reactive dilatation to cold which occurs in the fingers was not observed in the skin of the forehead.

Weatherby [13] reinvestigated the problem of the effect of smoking on the cutaneous temperature, taking into consideration certain physical and physiologic factors which had been overlooked in other investigations. Under ordinary conditions the smoking of a cigaret by the average habitual smoker (who inhales) results in a rise in the systolic and diastolic blood pressure of 10 to 25 mm. of mercury, an increase in pulse rate of 5 to 20 beats per minute, a drop in the temperature of the skin of the finger of 2 to 5 degrees C. (3.6 to 6 degrees F.) and of the toes of 3 to 7 C. (5.4 to 12.6 degrees F.). Occasionally greater changes occur in hyperactive subjects. The smoking of a cigaret by the average nonsmoker (without inhaling) causes only slight changes at most. The maximum vasoconstriction rarely persists for more than a few minutes. An environmental temperature of 30 C. inhibits almost completely the peripheral vasoconstriction caused by smoking. Smoking will also delay the warming of the skin of the feet after a cold foot bath. Drinking cold water has the same effect. Nicotine was shown to be the most important agent in causing these changes, as when it was completely removed from the cigaret none of the phenomena just mentioned occurred and when it was restored to the original cigaret they were again noted. The author was unable to lower the temperature of the skin by altering the nature of the respiratory movement, but various physiologic and psychic stimuli, such as reading, talking, hearing sudden noises, drinking cold water and hyperventila-

11. Hertzman, A. B., and Roth, L. W.: The Vasomotor Components in the Vascular Reactions in the Finger to Cold, Am. J. Physiol. **136**:669 (June) 1942.

12. Hertzman, A. B., and Roth, L. W.: The Absence of Vasoconstrictor Reflexes in the Forehead Circulation: Effects of Cold, Am. J. Physiol. **136**:692 (June) 1942.

13. Weatherby, J. H.: Skin Temperature Changes Caused by Smoking and Other Sympathomimetic Stimuli, Am. Heart J. **24**:17 (July) 1942.

tion, may cause changes in cutaneous temperature comparable to those produced by smoking. Mild physical activity, even at relatively low atmospheric temperatures, inhibits the fall in cutaneous temperature after smoking. The author concluded from these studies that it is difficult to determine what effect smoking has on the average person, since the conditions under which a person lives are not comparable to the conditions in the laboratory or the hospital where the experiments are performed.

Blood Flow.—Abramson, Fierst and Flachs [14] studied the rate of peripheral blood flow in a series of 19 patients who had edema either in a single upper or lower extremity or in both lower limbs. As in previous studies, the venous occlusion plethysmograph method was used. Separate measurements were made in the hand, forearm and leg. They noted that the peripheral circulation in edematous extremities unassociated with organic heart disease was mainly increased and certainly not decreased. When the edema was associated with congestive heart failure the readings on the edematous limbs fell within the range of those obtained for normal subjects. The authors are of the opinion that anoxia resulting from the edema or from the accumulation of vasodilator substances locally or from both of these factors might be effective in producing arteriolar vasodilatation and an increase in blood flow to the part.

The same authors,[15] using the same method of study, noted the rate of peripheral blood flow during rest and the circulatory response to exercise in a series of 25 patients with aortic insufficiency and in 16 subjects with mitral valvular disease. The average circulation in the hand was found to be somewhat diminished in both series of patients, while the readings for the forearm and leg fell within normal limits. The postexercise response of the blood vessels in the forearm to a specific amount of work was found to be greater than in the control group. The authors thus concluded that in the majority of patients with aortic insufficiency or mitral valvular disease there is no evidence to be found of excessive vasodilatation or vasoconstriction in the vessels of the forearm or leg.

Abramson and his associates [16] also demonstrated that the blood flow in the paralyzed limbs of 27 subjects with acute or chronic anterior poliomyelitis was the same as in the contralateral normal extremity. Evidence is presented, moreover, to substantiate the knowledge that the vessels of the diseased limb were more sensitive to cold than those of the normal limb. In a similar manner, Abramson, Fierst and Flachs [17] studied the peripheral circulation in 11 patients with various types of anemia. A moderate increase in blood flow was observed in the forearm, but in the hand the readings were, for the most part, within the lower range of normal or somewhat decreased. Studies of blood flow were also performed on 9 patients after the administration of mecholyl chloride (acetylbetamethylcholine chloride) by iontophoresis.[18] A significant increase in the rate of blood flow in the

14. Abramson, D. I.; Fierst, S. M., and Flachs, K.: Rate of Peripheral Blood Flow in the Presence of Edema, Am. Heart J. **25**:328 (March) 1943.

15. Abramson, D. I.; Fierst, S. M., and Flachs, K.: Effect of Muscular Exercise upon the Peripheral Circulation in Patients with Valvular Heart Disease, J. Clin. Investigation **21**:747 (Nov.) 1942.

16. Abramson, D. I.; Flachs, K.; Freiberg, J., and Mirsky, I. A.: Blood Flow in Extremities Affected by Anterior Poliomyelitis, Arch. Int. Med. **71**:391 (March) 1943.

17. Abramson, D. I.; Fierst, S. M., and Flachs, K.: Resting Peripheral Blood Flow in the Anemic State, Am. Heart J. **25**:609 (May) 1943.

18. Abramson, D. I.; Fierst, S. M., and Flachs, K.: Evaluation of the Local Vasodilator Effect of Acetyl-Beta-Methylcholine Chloride (Mecholyl) by Iontophoresis, Am. Heart J. **23**:817 (June) 1942.

forearm and the foot was noted, which continued for some time after the treatment was terminated. The effect on the leg was less marked. The increase in flow was considered to be primarily the result of vasodilatation of cutaneous blood vessels, those in the muscles probably contributing little if at all to the effect.

Lastly, Abramson and Fierst [19] studied the arterial blood flow in patients with uncomplicated varicose veins. The flow was found to fall within the range for normal subjects or somewhat beyond it. The authors are of the opinion that the various cutaneous lesions associated with varicosities do not have their origin in a diminished arterial inflow.

Friedland, Hunt and Wilkins [20] were unable to find an increased blood flow in a limb during rises in venous pressure. In this study the blood flow in the extremities of human beings was measured with and without local venous congestion produced by inflating blood pressure cuffs on the proximal parts of the limb. Four different methods were used: capillary microscopy, venous blood oxygen analysis, measurements of cutaneous skin temperature and determinations with the plethysmograph. The observations presented in this paper have undoubtedly caused considerable discussion and are contrary to the current opinion at this time, but they are lending support to a small but growing group of investigators who doubt the efficiency of the intermittent venous occlusion type of therapy. The stretching effect on the venocapillary bed, however, is readily demonstrated.

Evans and Stewart [21] report their measurements of the peripheral blood flow on a patient with an adrenal pheochromocytoma before operation and at intervals for one year afterward. They used the method previously described by Stewart and Jack and by Stewart and Evans for their determinations. Postoperatively the patient had an average increase of 60 per cent in the amount of blood allotted to the peripheral circulation. The basal metabolic rate decreased from plus 48 to an average of minus 15 after the operation. Additional studies revealed a longer circulation time, an increased cutaneous temperature, a decreased rectal temperature and a fall in blood pressure and in pulse rate following the operation.

Warren and his colleagues [22] studied the blood flow in the arm of a normal person in whom procaine hydrochloride had been injected by the paravertebral route into the sympathetic ganglions supplying the right upper extremity. Observations were made on two separate occasions, and measurements were taken before, during and after the anesthetization. Complete absence of vasomotor activity in response to sensory stimuli or deep inspiration indicated complete paralysis of the sympathetic ganglions supplying the right hand. This paralysis produced a striking increase in blood flow. After the effect of the procaine had passed away, the right hand was immersed in water at a temperature of 43 C. Local heat produced the same increase in blood flow in the right hand as had paralysis of the sympathetic ganglions. The fact that a complete blocking of the sympathetic ganglions produces full vasodilatation in the hand demonstrated to the authors that inhibition of sympathetic activity is sufficient to explain the vasodilatation

19. Abramson, D. I., and Fierst, S. M.: Arterial Blood Flow in Extremities with Varicose Veins, Arch. Surg. **45**:964 (Dec.) 1942.

20. Friedland, C. K.; Hunt, J. S., and Wilkins, R. W.: Effects of Changes in Venous Pressure upon Blood Flow in the Limbs, Am. Heart J. **25**:631 (May) 1943.

21. Evans, W. F., and Stewart, H. J.: The Peripheral Blood Flow in a Case of Adrenal Pheochromocytoma Before and After Operation, Am. Heart J. **24**:835 (Dec.) 1942.

22. Warren, J. V.; Walter, C. W.; Romano, J., and Stead, E. A., Jr.: Blood Flow in the Hand and Forearm After Paravertebral Block of the Sympathetic Ganglia: Evidence Against Sympathetic Vasodilator Nerves in the Extremities of Man, J. Clin. Investigation **21**:665 (Nov.) 1942.

which occurs in the hand when the body is heated. The authors saw no necessity for postulation that the sympathetic nerves to the hand contain vasodilator fibers.

In the forearm, paravertebral injection of procaine hydrochloride into the sympathetic ganglions caused a sixfold increase in blood flow. A similar increase in blood flow was produced by immersing the forearm in hot water. This indicates again that the removal of all sympathetic impulses to the vessels of the forearm produces as great rise in blood flow as does heating the part. Inhibition of vasoconstriction alone can explain the phenomenon. The fact that neither heating the forearm nor injection of procaine into the sympathetic ganglions produced maximal dilatation in the forearm indicated to the authors that many of the vessels of the forearm are not under the control of the sympathetic nervous system. They suggested that the vessels of the skin of the forearm are under the control of the sympathetic nervous system and that those of the muscle are not.

Diagnostic Tests.—Goetz [23] describes a new ergograph with which a claudication index can be ascertained. Studies were made on normal persons as well as on patients with intermittent claudication. For 97 per cent of those with claudication the index was below 40. This apparatus appears simple, and the claudication index affords considerable opportunity for investigators interested in evaluating various therapeutic agents.

Circulation Time.—Hussey, Cyr and Katz [24] compared solutions of alpha lobeline, calcium gluconate and magnesium sulfate for purposes of measuring the circulation time from the arm to the tongue. The measurements were made on 50 normal persons and on 50 patients with heart failure. Alpha lobeline gave somewhat shorter measurements than calcium gluconate and magnesium sulfate for both groups of subjects but failed to provide an end point more often than either of the other drugs. Furthermore, the fact that it sometimes measured the arm to lung circulation time seems to detract from its value for routine use. Its chief advantage consists in the objectivity of its end point. Calcium gluconate and magnesium sulfate gave approximately equal results. They seem to be equally valuable for routine use in measurements of the arm to tongue circulation time, and perhaps are more valuable in this respect than alpha lobeline.

Elek and Solarz [25] have added papaverine to the numerous agents used for measuring circulation time in man. They consistently obtained a sudden deep inspiration after the injection of 40 mg. (1.25 cc.) of papaverine hydrochloride intravenously. The arm–respiratory center circulation time was thus obtained, as with sodium cyanide. The average time for 50 normal persons without evidence of heart failure was 20.8 seconds, the range extending from 15.4 to 27.0 seconds.

Wilburne [26] reinvestigated the problem of the effects of posture on the circulation time, using calcium gluconate and measuring the velocity of blood flow from the arm to the tongue. In his studies, the time was measured with the patient in the recumbent position and again with the patient comfortably sitting with both

23. Goetz, R. H.: Ergographic Studies: Description of New Device, and Observations on Normal Subjects and on Patients with Intermittent Claudication, Am. Heart J. **23**:782 (June) 1942.

24. Hussey, H. H.; Cyr, D. P., and Katz, S.: The Comparative Value of Calcium Gluconate, Magnesium Sulfate, and Alpha Lobeline Hydrochloride as Agents for Measurements of the Arm to Tongue Circulation Time in Fifty Patients With and Fifty Patients Without Heart Failure, Ann. Int. Med. **17**:849 (Nov.) 1942.

25. Elek, S. R., and Solarz, I. D.: The Use of Papaverine as an Objective Measure of Circulation Time, Am. Heart J. **24**:821 (Dec.) 1942.

26. Wilburne, M.: The Effects of Posture on the Velocity of Blood Flow from Arm to Tongue, Am. Heart J. **24**:816 (Dec.) 1942.

legs dependent over the edge of the bed. A total of 73 measurements were taken. Two types of results were obtained. For patients whose circulation time in the recumbent position is normal, the value in the sitting position is higher, whereas for persons whose circulation time in the recumbent position is prolonged, the time in the upright position tends to be lower. The author believes that these findings substantiate the observations that the minute cardiac output is less in the sitting and standing positions than in the recumbent position. In the patients who already have a prolonged circulation time in the recumbent position, especially those with congestive heart failure, a change in position to the upright produces a pooling of blood in the lower extremities, lessens pulmonary congestion and decreases the circulation time.

DICOUMARIN

Link and his associates [27] were the first to isolate an active hemorrhagic agent from spoiled sweet clover, which is now known as dicoumarin (3,3′-methylene-bis-[4-hydroxycoumarin]). Henceforth in this review it will be referred to as dicoumarin. This is a white crystalline substance slightly soluble in water but readily soluble in alkaline solution. The chemical experiments on it are too numerous to include in this review and will be omitted. Considerable pharmacologic and clinical studies have been reported, and these will be briefly reviewed.

This compound has been administered to hundreds of laboratory animals and used clinically on a large number of human beings and the reported results have been fairly consistent.[28] The authors agree that the effect of dicoumarin appears to be on prothrombin only. There is usually an associated delay in the coagulation time. The substance is active whether given orally or intravenously, and there is usually a lag of from twenty-four to seventy-two hours before the action of the drug is measurable. Fresh transfusions of serum or whole blood will cause a

27. Campbell, H. A., and Link, K. P.: Studies on the Hemorrhagic Sweet Clover Disease: IV. The Isolation and Crystallization of the Hemorrhagic Agent, J. Biol. Chem. **138**: 21 (March) 1941. Stahmann, M. A.; Huebner, C. F., and Link, K. P.: Studies on the Hemorrhagic Sweet Clover Disease: V. Identification and Synthesis of the Hemorrhagic Agent, ibid. **138**:513 (April) 1941.

28. (*a*) Bingham, J. B.; Meyer, O. O., and Pohle, F. J.: Studies on the Hemorrhagic Agent 3,3′-Methylene-Bis-(4-Hydroxycoumarin): I. Effect on the Prothrombin and Coagulation Time of the Blood of Dogs and Humans, Am. J. M. Sc. **202**:563 (Oct.) 1941. (*b*) Meyer, O. O.; Bingham, J. B., and Pohle, F. J.: The Effect of the Synthetic Dicoumarin 3,3′-Methylene-Bis-(4-Hydroxycoumarin) on the Prothrombin Time and Coagulation Time, J. A. M. A. **118**:1003 (March 21) 1942. (*c*) Butt, H. R.; Allen, E. V., and Bollman, J. L.: A Preparation from Spoiled Sweet Clover [3,3′-Methylene-Bis-(4-Hydroxycoumarin)] Which Prolongs Coagulation and Prothrombin Time of the Blood: Preliminary Report of Experimental and Clinical Studies, Proc. Staff Meet., Mayo Clin. **16**:388 (June 18) 1941. (*d*) Barker, N. W.; Butt, H. R.; Allen, E. V., and Bollman, J. L.: The Effect of 3,3′-Methylene-bis (4-Hydroxycoumarin) on Blood Coagulation Factors, J. A. M. A. **118**:1003 (March 21) 1942. (*e*) Allen, E. V.; Barker, N. W., and Waugh, J. M.: A Preparation from Spoiled Sweet Clover [3,3′-Methylene-Bis-(4-Hydroxycoumarin)] Which Prolongs Coagulation and Prothrombin Time of the Blood: A Clinical Study, ibid. **120**:1009 (Nov. 28) 1942. (*f*) Prandoni, A., and Wright, I.: The Anti-Coagulants, Bull. New York Acad. Med. **18**:433 (July) 1942. (*g*) Wright, I. S., and Prandoni, A.: The Dicoumarin 3,3′-Methylene-Bis-(4-Hydroxycoumarin): Its Pharmacologic and Therapeutic Action in Man, J. A. M. A. **120**:1015 (Nov. 28) 1942. (*h*) Butsch, W. L., and Stewart, J. D.: Clinical Experiences with Dicoumarin: 3,3′-Methylene-Bis-(4-Hydroxycoumarin), ibid. **120**:1025 (Nov. 28) 1942. (*i*) Townsend, S. R., and Mills, E. S.: Effect of Synthetic Haemorrhagic Agent, 3,3′-Methylene-Bis-(4-Hydroxycoumarin), in Prolonging Coagulation and Prothrombin Time in Human Subject, Canad. M. A. J. **46**:214 (March) 1942. (*j*) Davidson, C. S., and MacDonald, H.: An Evaluation of the Use of Dicoumarin [3,3′-Methylene-Bis-(4-Hydroxycoumarin)] as an Anticoagulant and Its Effect on Certain Plasma Constituents, J. Clin. Investigation **21**:644 (Sept.) 1942.

prompt lowering of the prothrombin and coagulation times, but occasionally this effect is not sustained and several transfusions may be necessary. Vitamin K has no effect on its prothrombin activity.

Pharmacologic studies reveal that it has no effect on hepatic or renal function, blood sugar, the erythrocyte or leukocyte count, the concentration of bilirubin or calcium in the blood serum, the value for nonprotein nitrogen in the blood, the icterus index, the fragility of the erythrocytes or the number of blood platelets. The sedimentation rate is usually increased, and the clot retraction is occasionally retarded. The bleeding time is not influenced, and although small doses have no influence on the coagulation time, larger doses tend to prolong it. There is considerable controversy as to the effect of this substance on the liver, especially after prolonged administration of fatal doses. When it has been administered correctly no demonstrable clinical evidence of hepatic disease has been noticed. Bingham, Meyer and Pohle [28b] report only moderate hydropic degeneration of the liver when fatal doses of dicoumarin were given. Rose, Harris and Chen [29] found central necrosis of the liver in about one half of the rats which had died of fatal doses. Postmortem studies made by Richards and Cortell [30] on a group of dogs, monkeys and guinea pigs that had received dicoumarin revealed necrosis of the liver. On the other hand, animals dying of spoiled sweet clover disease show no evidence of pathologic change in the liver. The majority of authors agree that the drug produces little, if any, damage to the liver and that when such damage is present it is usually secondary to local hemorrhage.

The mechanism by which dicoumarin causes hemorrhage appears to be fairly conclusive. It inhibits the action of prothrombin by destroying it or by inhibiting its production. If enough dicoumarin is given, the coagulation time is prolonged and bleeding may develop. It produces a hemorrhagic syndrome unlike any other type. Wright and Prandoni [28g] studied a number of patients who had received sufficient dicoumarin to produce this hemorrhagic tendency. They found the incidence of toxic reactions to be uninfluenced by age, sex or malnutrition. There was no increase in capillary fragility, no change in gastric acidity and no disturbance in renal or hepatic function. Davidson and MacDonald [31] were likewise unable to find a relationship between this abnormal clotting mechanism and other coagulation factors, namely: foreign surface, platelets, "globulin substance" and plasma proteolytic enzyme. Like other investigators of this drug, they were unable to find any effect on the picture of the blood, hepatic function or plasma proteins. McGinty, Seegers, Pfeiffer and Loew [32] noted that purified beef prothrombin was capable of counteracting the hypoprothrombinemia induced in dogs by oral administration of dicoumarin. These authors considered the phenomena as purely a method of replacing the prothrombin, as the beef substance was as easily destroyed as the dogs' own plasma prothrombin.

The doses used by the various authors have been somewhat similar. Bingham and Meyer [28b] advise an initial dose of 5 mg. per kilogram followed by daily administration of 1.5 mg. per kilogram. They found that 4 mg. per kilogram at intervals

29. Rose, C. L.; Harris, P. N., and Chen, K. K.: Toxicity of 3,3'-Methylene-Bis-(4-Hydroxycoumarin), Proc. Soc. Exper. Biol. & Med. **50**:228 (June) 1942.

30. Richards, R. K., and Cortell, R.: Studies on Anticoagulant 3,3'-Methylene-Bis-(4-Hydroxycoumarin), Proc. Soc. Exper. Biol. & Med. **50**:237 (June) 1942.

31. Davidson, C. S., and MacDonald, H.: A Critical Study of the Action of 3,3'-Methylene-Bis-(4-Hydroxycoumarin) (Dicoumarin), Am. J. M. Sc. **205**:24 (Jan.) 1943.

32. McGinty, D. A.; Seegers, W. H.; Pfeiffer, C. C., and Loew, E. R.: Plasma Prothrombin Concentration in Dogs Given 3,3'-Methylene-Bis-(4-Hydroxycoumarin) and Purified Beef Prothrombin, Science **96**:540 (Dec. 11) 1942.

of three to five days was adequate to increase the prothrombin time when given intravenously. The latter method of administration was not recommended, as it has no advantage over the oral route and does not shorten the latent period. Allen and his colleagues [28e] administered 200 to 300 mg. on the first day, 200 mg. on the second and additional on the third day if the prothrombin time warrants it. Wright and Prandoni [28g] administered 200 mg. daily for three days, at which time an adequate prothrombin time was noted. Butsch and Stewart [28h] used 300 mg. on two successive days and obtained the desired results. Two hundred milligrams on two successive days was recommended for children. Frequent determinations of prothrombin time are necessary and readings in excess of thirty-five seconds or 25 per cent of normal are unwise. Optimum levels are between thirty and thirty-five seconds, and if the level falls below thirty seconds a dose is indicated. The early signs of toxicity are usually lassitude and general malaise, and these are followed later by hemorrhagic tendencies. With the aforementioned methods of administration the prothrombin time can be expected to remain prolonged from seven to ten days. When rapid anticoagulation is desired, combined administration of heparin and dicoumarin is advisable. When the two substances are used together, the heparin is given intravenously and discontinued at the end of the latent period for dicoumarin. As heparin has no effect on the prothrombin time, this period is easily ascertained.

Stats and Bullowa [33] noted the effect of a single dose of dicoumarin on 39 patients. The dosage varied from 400 mg. for patients weighing 130 pounds (58.5 Kg.) or less and 600 mg. to patients weighing over 160 pounds (72 Kg.). They noted a prolongation of the coagulation time and a lowering of the prothrombin index of the blood for approximately six days, beginning between twenty-four and seventy-two hours after the drug was administered. At the height of the action of the drug the coagulation time varied between sixteen and forty-two minutes, in most cases being between twenty-two and twenty-six minutes. The prothrombin index varied from 100 per cent to 10 per cent of normal.

There seems to be little doubt that dicoumarin prevents intravascular thrombi. Dale and Jacques [34] were among the first to demonstrate this phenomenon in dogs. In one series of dogs thrombosis was produced successfully by crushing the vein, whereas among dogs receiving dicoumarin 60 per cent were completely free of thrombi. In another series, thrombosis was prevented in a series of glass cells inserted between the carotid artery and the jugular vein. Bollman and Preston [35] confirmed this when they noted that glass cannulas interposed between two ends of an artery are seldom occluded by thrombi when animals have received dicoumarin. Richards and Cortell [30] found that dicoumarin greatly reduced the incidence and degree of thrombus formation following the intravenous injection of ethanolamine oleate.

The indications for the use of dicoumarin are similar to those of heparin. Its chief advantages over heparin are its ease of administration and its low cost. Its main disadvantage is the prolonged action after administration of the drug is discontinued. It is used therapeutically in an effort to prevent arterial and venous thrombosis. It has been used in cases of pulmonary embolism and infarction,

33. Stats, D., and Bullowa, J. G. M.: Effect of Single Dose of 3,3'-Methylene-Bis-(4-Hydroxycoumarin) upon Blood Coagulation in Humans, Proc. Soc. Exper. Biol. & Med. **50**:66 (May) 1942.

34. Dale, D. U., and Jacques, L. B.: The Prevention of Experimental Thrombosis by Dicoumarin, Canad. M. A. J. **46**:546 (June) 1942.

35. Bollman, J. L., and Preston, F. W.: The Effects of Experimental Administration of Dicoumarin, J. A. M. A. **120**:1021 (Nov. 28) 1942.

preoperative and postoperative thrombophlebitis, various peripheral vascular disorders, acute coronary thrombosis and subacute bacterial endocarditis. Barker, Allen and Waugh [36] used it in 497 surgical cases in which vascular complications seemed likely. In only 4 cases did thrombosis or embolism develop, and in 3 of these it was difficult to secure a satisfactory increase in prothrombin time. Hemorrhage was a complication in 47 of these cases, but it was minor in 29 and moderate to severe in only 18 (fatal in only 1). Bingham, Meyer and Howard [37] gave dicoumarin to 105 patients and found it satisfactory and safe. They administered 10 Gm. over a ninety day period to a patient with thromboangiitis obliterans and obtained symptomatic improvement. Lehmann [38] has used it successfully in Sweden, where is is known as A P (antiprothrombin). Butsch and Stewart have also used dicoumarin extensively. In a recent article [39] they report administering it to 23 male patients one or two days prior to doing a herniorrhaphy. The operation was completed without complications, as excessive bleeding was not encountered and healing occurred as normally expected. The purpose of this study was to demonstrate the safety of the drug when given preoperatively, especially to patients in whom postoperative complications are anticipated. Lastly, DeBakey,[40] in a recent editorial, warns against overenthusiasm in the prevention of postoperative vascular accidents with anticoagulants in general, reminding his readers of the normally low incidence of these complications.

There are certain definite contraindications to the use of dicoumarin. It should not be given to patients with renal insufficiency, purpura of any type, a blood dyscrasia with a tendency to bleeding, existing prothrombin deficiency (such as may occur in jaundice due to hepatic disease or malnutrition) or, lastly, subacute bacterial endocarditis. It is needless to mention its contraindication for patients with ulcerative or open lesions or with continuous gastric drainage or persons for whom a surgical operation is contemplated during the next two weeks.

ARTERIOSCLEROSIS

Lake and his colleagues [41] report their observations on the relationship of arteriosclerosis and varicose veins to the occupational activities of employees in a large department store. Five hundred and thirty-six persons were studied who had been at a particular type of work for ten years or more. They were grouped according to age and according to the manner in which they worked, namely: standing, sitting, walking or climbing stairs. All of these persons were over 40 years of age; 305 were men and 231 women. The criteria for diagnosis

36. Barker, N. W.; Allen, E. V., and Waugh, J. M.: The Use of Dicoumarol [3,3'-Methylene-Bis-(4-Hydroxycoumarin)] in the Prevention of Postoperative Thrombophlebitis and Pulmonary Embolism, Proc. Staff Meet., Mayo Clin. **18**:102 (April 7) 1943.

37. Bingham, J. B.; Meyer, O. O., and Howard, B.: Studies on the Hemorrhagic Agent 3,3'-Methylene-Bis-(4-Hydroxycoumarin): III. A Report on Further Clinical Observations, Am. J. M. Sc. **205**:587 (April) 1943.

38. Lehmann, J.: Hypoprothrombinemia Produced by Methylene-Bis-(4-Hydroxycoumarin): Its Use in Thrombosis, Lancet **1**:318 (March 14) 1942; Hypo-Prothrombinemia Produced by 3,3'-Methylene-Bis-(4-Hydroxycoumarin) and Its Use in the Treatment of Thrombosis, Science **96**:345 (Oct. 9) 1942.

39. Butsch, W. L., and Stewart, J. D.: Administration of Dicoumarin Compound for Prophylaxis of Postoperative Thrombosis and Embolism: A Preliminary Report, Arch. Surg. **45**:551 (Oct.) 1942.

40. DeBakey, M.: Dicoumarin and Prophylactic Anticoagulants in Intravascular Thrombosis, Surgery **13**:456 (March) 1943.

41. Lake, M.; Pratt, G. H., and Wright, I. S.: Arteriosclerosis and Varicose Veins, J. A. M. A. **119**:696 (June 27) 1942.

were a history of intermittent claudication, finding of rubor on dependency and pallor on elevation, absence of pulse, low oscillometric readings after release of any abnormal spasm, and evidence of arteriosclerosis as shown by roentgenograms. Forty-six per cent of the men and 20 per cent of the women were found to have evidence of arteriosclerosis by these criteria. In 177 arteriosclerosis was noted roentgenologically, and it was the sole evidence of arteriosclerosis in 147. The oscillometer revealed little evidence of pathologic change in the group as a whole, but it was responsible for detecting a larger percentage of arterial disease in women than in men. Statistical differences were more significant in the younger age group (40 to 49). In this group, stair climbing produced a higher incidence of arteriosclerosis than did standing, sitting or walking. Over the age of 50 little difference was noted in the occupational incidence. The use of tobacco and alcohol had no influence in the occurrence of arteriosclerosis in this series. A relationship was found to exist between the incidence of hypertension and that of arteriosclerosis of the lower extremities. Women showed a much higher incidence of varicose veins than men employed at the same occupation. This difference held true even when the factor of pregnancy was removed from the data. Women who had been pregnant showed a higher occurrence of varicose veins than women who had never been pregnant. Varicose veins were common in this series, being noted in 40.7 per cent of men and 73.2 per cent of women. Women who stood or walked showed a higher incidence of varicose veins than those who sat at their work. This was not noted in men. It is interesting that the incidence of arteriosclerosis of the leg arteries in men was higher in those with varicose veins, but this could not be statistically established for women.

Sappington and Fisher [42] report on the vascular lesions of 44 amputated gangrenous legs. The specimens were obtained from patients with arteriosclerosis obliterans. The gross study revealed an extraordinary amount of arterial occlusion, averaging 44 per cent of the entire length of the anterior tibial, posterior tibial and peroneal arteries. The average number of vessels occluded per case was two and three-tenths. The occluding lesions apparently represented various stages and regressions of organizing obstructive clots. Atheroma did not appear to be a participating feature, as vessels with the highest incidence of atheroma exhibited the lowest percentage of occlusions while those with the highest incidence of closure presented the least degree of atheromatous development. Calcification was found to be the outstanding lesion in the media. It was demonstrated in 100 per cent of 38 cases roentgenologically and in 98 per cent of 44 cases microscopically. Bone formation in the media of the peripheral arteries was found in 70 per cent of the cases. The authors expressed the opinion, on the basis of their studies, that the attempt at bone formation in a large part precedes and does not follow calcareous deposition in the media.

Dauber and Katz [43] were able to produce atheromatous vascular lesions in chicks by feeding the birds an adequate diet plus 2.5 to 5 per cent of cholesterol in cottonseed oil. Atheromatosis developed rather rapidly, usually beginning on the forty-second day. In this study a group of 24 cockerels 10 days old were studied, of which half were used as controls. In none of the latter group did vascular lesions develop. In 7 of the 12 cholesterol-fed birds atheromatous deposits developed in the aorta. Of these 7 chicks, 3 had intimal atheromatous lesions in the coronary

42. Sappington, S. W., and Fisher, H. R.: Arteriosclerosis Obliterans, Arch. Path. **34**:989 (Dec.) 1942.

43. Dauber, D. V., and Katz, L. N.: Experimental Cholesterol Atheromatosis in an Omniverous Animal, the Chick, Arch. Path. **34**:937 (Dec.) 1942.

arteries with resultant narrowing of the lumens of the vessels. In 2 of the 7, similar changes were noted in the splenic arteries. Unfortunately, only a small number of chicks were studied, but it is significant that the pathologic changes which were produced resembled those found in older chickens. It also lends support to those investigators who experimentally produced atheroma in rabbits and other animals with cholesterol.

Hueper [44] has continued his studies on the relationship between physicochemical colloidal disturbances of the plasma and the development of vascular atheromatosis and organic thesaurosis. In this study the colloidal solutions of pectin, a macromolecular carbohydrate, were injected intravenously into rabbits and dogs and the effects on the blood and the internal organs were noted. The solutions were either freshly prepared or autoclaved. The immediate effects produced on the blood by either type were a colloidoclastic leukopenia, acceleration of erythrocytic sedimentation and a moderate shortening of clotting time. When the freshly prepared solutions of pectin were injected into the animals, not only did a marked foam cell storage phenomenon develop in the spleen, kidneys and bone marrow, but a foam cell atheromatosis of various arteries was also noted. Older vascular lesions of this origin are characterized by hyaline intimal thickening with or without calcification and by hyaline necrosis and calcification in the media underneath. When the autoclaved pectin solutions were injected only minor changes were noted in the previously mentioned organs. The author explains this difference by the fact that heat will markedly depolymerize pectin solutions and will thereby destroy much of their macromolecular characteristics and original physicochemical properties.

Schlossmann [45] demonstrated that the fibrinoid material within arteriosclerotic aortas and peripheral vessels of the lower extremities was not a true serum fibrin. This was done by subjecting the material to tryptic digestion. He also presents evidence to show that the fibrinoid substance in these vessels was partially necrotic collagen.

THROMBOANGIITIS OBLITERANS

The dynamics of blood flow in 7 patients with thromboangiitis obliterans was studied by Landowne.[46] Measurements were made by the plethysmographic method. The resting blood flow in the horizontal position in the feet of these patients was found to be within normal limits, but the maximal volume flow of blood consequent to certain dilating procedures was found to be less than that observed in normal persons. These conclusions were drawn from the observation that after the release of arterial occlusion in the thigh an initial decrease in blood flow was noted and could not be prevented by local heat or by sympathetic ganglionectomy. Although there was no evidence to indicate that the dilating procedures which were used did not produce dilatation of the small vessels, the author considers the possibility that these procedures may evoke abnormal responses in this disease, both qualitatively and quantitatively. The initial decrease in blood flow consequent to release of arterial occlusion may be caused by the factor just mentioned, by a peripheral vasoconstrictor effect of ischemia or, most likely, by a local constrictive response of the major vessels. Since the last two factors may be active in the normal subject, this constrictive response need not of necessity be caused by thromboangiitis obliterans, but at least it becomes manifest in this disease.

44. Hueper, W. C.: Experimental Studies in Cardiovascular Pathology: V. Pectin Atheromatosis and Thesaurosis in Rabbits and in Dogs, Arch. Path. **34**:883 (Nov.) 1942.

45. Schlossmann, N. C.: Fibrinoid Necrosis in Arteriosclerosis, Arch. Path. **34**:365 (Aug.) 1942.

46. Landowne, M.: Dynamics of Blood Flow in Thromboangiitis Obliterans, Am. Heart J. **24**:50 (July) 1942.

Jahsman and Durham [47] caution the physicians examining young men of draft age to be on the alert for thromboangiitis obliterans, especially if men complain of symptoms referable to the circulation. In seven months the authors encountered 7 such persons. One foot or leg was invariably more involved than the other. In some cases the symptoms were only in one digit. None of the subjects showed complete occlusion of the larger arteries.

Mills [48] reports an interesting case history of a man 37 years of age who complained of aching and numbness in the left calf on walking. On physical examination he was found to have occlusive vascular disease in the left leg. Prior to this illness the patient had used a pneumatic hammer in drilling rock and was in the habit of pressing the hammer down with his left foot. The leg was subsequently amputated, and the author received the report that the pathologic picture was compatible with thromboangiitis obliterans.

GLOMUS TUMORS

Glomus tumors are reported by Loeb,[49] Scully [50] and Ottley.[51] No new ideas are presented.

PERIARTERITIS NODOSA

Very little has been added to the knowledge of periarteritis nodosa during the past year, excepting some additional evidence of the role of hypersensitivity in its causation, presented by Rich.[52] Additional cases are reported by ten groups of authors, but they will not be mentioned.

Krupp [53] uses the term "visceral angiitis" to designate the group of disorders featured by peculiar lesions of small arteries, namely: periarteritis nodosa, lupus erythematosus disseminata, Libman-Sacks disease and the syndromes described by Friedberg and Gross. He studied a series of 21 cases of this type, with special emphasis on quantitative studies of the urinary sediment by the method of Addis. In 7 cases no specific change in urinary sediment was discovered, but in 14 cases a singular picture of the sediment was observed. The uniqueness of this picture lies in the presence of red blood cells, red cell casts, oval fat bodies, fatty casts, broad casts and abnormal quantities of protein in the same specimen of urine. The author differentiates the urinary picture from glomerulonephritis and other renal disorders, considering the unusual sediment to be of diagnostic value in doubtful cases of the disorders just mentioned.

THROMBOPHLEBITIS

A fatal case of thrombophlebitis migrans is reported by Birnberg and Hansen.[54] The disease developed in a 14 year old boy who ultimately died of mesenteric thrombosis. Treatment with heparin was not successful. Bacteriologic studies gave

47. Jahsman, W. E., and Durham, R. H.: Recognition of Incipient Thromboangiitis Obliterans in Young Draftees, Ann. Int. Med. **18**:164 (Feb.) 1943.

48. Mills, J. H.: Pneumatic Hammer Disease in Unusual Location, Northwest Med. **41**:282 (Aug.) 1942.

49. Loeb, M. J.: Glomus Tumor: Report of a Case, J. Florida M. A. **29**:372 (Feb.) 1943.

50. Scully, J. C.: Glomus Tumor, or Glomangioma, J. Michigan M. Soc. **42**:118 (Feb.) 1943.

51. Ottley, C. M.: Glomus Tumor, Brit. J. Surg. **29**:387 (April) 1942.

52. Rich, A. R.: Additional Evidence of the Role of Hypersensitivity in the Etiology of Periarteritis Nodosa, Bull. Johns Hopkins Hosp. **71**:375 (Dec.) 1942.

53. Krupp, M. A.: Urinary Sediment in Visceral Angiitis (Periarteritis Nodosa, Lupus Erythematosus, Libman-Sacks "Disease"), Arch. Int. Med. **71**:54 (Jan.) 1943.

54. Birnberg, V. J., and Hansen, A. E.: Thrombophlebitis Migrans, J. Pediat. **21**:775 (Dec.) 1942.

no clue to the underlying cause. An allergic phenomenon was suggestive when the microscopic study revealed an eosinophilic inflammation and swelling of the intima of an involved vein.

Hirschboeck and Coffey [55] studied 10 patients who had pulmonary emboli. They considered not only the hemodynamic factors, and local trauma to tissues and blood vessels as etiologic agents in the development of phlebothrombosis and pulmonary emboli, but also anemia and elevation of blood fibrinogen and platelet levels as of equal importance. These factors working together result in a rapid and powerful clot retraction. The strength and rapidity of clot retraction are perhaps responsible for the loosening of thrombi from vessel walls and explain the coincidence of short clot retraction times with the occurrence of pulmonary embolism. Small amounts of heparin greatly prolong the clot retraction time, and the authors believe that heparin should be used prophylactically for patients with short clot retraction times to reduce the incidence of pulmonary embolism.

Maynard and Hollinger [56] studied the platelet counts of 20 patients with vascular disorders of the lower extremities. The majority of these patients had unilateral edema secondary to a venous disorder, ulcer, Schamberg's disease or some other type of dermatitis. The platelet counts were usually lower in the blood of the affected extremity than in that from the opposite extremity or the lobe of an ear. As the local diminution in platelets often parallels the local clinical conditions, in the authors' opinion this laboratory procedure is of therapeutic and prognostic significance. Unfortunately the platelet counts were so variable that one questions the accuracy of the procedure.

VASOSPASTIC DISORDERS

Linenthal [57] reports 2 additional cases of pulmonary fibrosis associated with Raynaud's disease. One patient, under observation, showed pulmonary fibrosis by roentgenograms and studies of the pulmonary dynamics. The other, at postmortem examination, showed extensive pulmonary fibrosis, with changes in the small vessels of the lungs that were consistent with the vascular changes found in the small digital arteries in advanced stages of Raynaud's disease.

Three interesting cases of interstitial calcinosis circumscripta associated with scleroderma and Raynaud's disease were reported by Bercow and Poppel.[58] The changes were demonstrated by interesting roentgenograms.

The important roentgen features of scleroderma and acrosclerosis are also presented by Jackman.[59] These include calcinosis, pulmonary fibrosis and esophageal stenosis. The last two conditions are questionable. Jackman discusses scleroderma, stressing the generalized aspect of the disease.

PALMAR ERYTHEMA

Bean [60] reports his observations on 11 additional cases of palmar erythema and cutaneous vascular "spiders." In all of these cases there was a primary hepatic

55. Hirschboeck, J. S., and Coffey, W. L., Jr.: Clot Retraction Time in Thrombophlebitis and Pulmonary Embolism, Am. J. M. Sc. **205**:727 (May) 1943.

56. Maynard, M. T. R.: Thrombocyte Deficit: The Behavior of the Blood Platelets in Diseases of Vascular Stasis of the Extremities, J. A. M. A. **121**:1194 (April 10) 1943.

57. Linenthal, H.: Observations Concerning Pulmonary Fibrosis in Raynaud's Disease, New England J. Med. **227**:433 (Sept. 17) 1942.

58. Bercow, C., and Poppel, M. H.: Interstitial Calcinosis Circumscripta Associated with Scleroderma and Raynaud's Disease, Radiology **39**:96 (July) 1942.

59. Jackman, J.: Roentgen Features of Scleroderma and Acrosclerosis, Radiology **40**:163 (Feb.) 1943.

60. Bean, W. B.: Acquired Palmar Erythema and Cutaneous Vascular "Spiders," Am. Heart J. **25**:463 (April) 1943.

or pulmonary disease. In none of them was a familial history of palmar erythema obtained. Although the author has insufficient data to support his hypothesis, he is of the opinion that these localized vascular disturbances result from an abnormality in circulating estrogenic substances and other 17-keto steroids. Lofgren's observations [61] lend some support to this theory. He noted a palmar erythema in 3 pregnant women which promptly disappeared after delivery. In 1 patient's case an attempt was made to duplicate the condition about four months after delivery with large doses of estrogen. Although a slight flushing of the hands developed, it was not as striking as that noted while the patient was pregnant. Trostler [62] has come to a different conclusion on palmar erythema. He noted it in 22 cases of pulmonary tuberculosis and in 1 case of nontuberculous empyema. The erythema was found to consist of dilated vessels, and Trostler considers it secondary to circulating toxins, basing his conclusions on previous experimental work in which capillary dilatation was produced in laboratory animals with various bacterial toxins.

GANGRENE

Riordan and his colleagues [63] cite 3 cases of pellagra, all with unusual affected areas. Of interest in this review is the case in which local gangrene of the right great toe developed on the basis of a pellagrous dermatitis. The toe was amputated, and the other cutaneous manifestations responded to nicotinic acid.

TREATMENT

The treatment of certain vascular disorders is gradually undergoing revolutionary changes. The use of cold rather than heat has been found to be of value in the treatment of frostbite and immersion foot, and it appears likely that it may play a more prominent role in the therapy of other organic peripheral vascular disorders in the future. Bigelow,[64] in an excellent survey and discussion of the literature on the physiology and treatment of frostbite, expresses the belief that one should not neglect the specific therapy already shown to be useful by previous investigators. His conclusions were drawn from a review of the literature and not from clinical study. Many of the methods referred to by Bigelow are losing their popularity, especially in the treatment of occlusive vascular diseases.

Greene [65] has continued to advocate the use of cold in the treatment of frostbite, immersion foot and trench foot. He has designed a refrigerator for the treatment of these conditions but has not been able to give it a clinical trial. Like others, Greene considers that frostbite and immersion foot differ only in degree of exposure. In the former, capillary damage is so severe that destruction of tissue is inevitable and no amount of therapy will restore the necrotic element. The remaining viable tissue usually responds to a cool environment. In immersion foot and trench foot, the tissues are merely in a "state of chilling," and, although the capillaries are affected, reversible changes occur and healing can be expected.

Reports on successful treatment of peripheral vascular disease with endocrine products continue to make their appearance in the literature. These studies have

61. Lofgren, R. C.: Erythema of the Palms Associated with Pregnancy, Arch. Dermat. & Syph. **46**:502 (Oct.) 1942.

62. Trostler, L. S.: Erythema of the Extremities in Tuberculosis, Am. Rev. Tuberc. **47**:168 (Feb.) 1943.

63. Riordan, T. J.; Gellis, S., and Rubinowitz, A. M.: Unusual Sites of Lesions in Pellagra: Gangrene of the Toe in One Case, Arch. Dermat. & Syph. **46**:661 (Nov.) 1942.

64. Bigelow, W. G.: The Modern Conception and Treatment of Frostbite, Canad. M. A. J. **47**:529 (Dec.) 1942.

65. Greene, R.: Cold in the Treatment of Damage Due to Cold, Lancet **2**:695 (Dec. 12) 1942.

in general been poorly controlled. Periods of treatment have been of long duration, and objective evidence of improvement, with or without the aid of the various mechanical devices, has been meager. Subjectively, the patients usually feel better. Walker,[66] in a recent article on the effect of sex hormones in the treatment of various vascular disorders, included 14 patients with organic peripheral vascular diseases. These patients received androgenic and estrogenic substances. In this group 8 patients showed marked improvement, 2 responded fairly well and 4 were not benefited. In 2 patients, with characteristic thromboangiitis obliterans, the results were unusually good. Beaser and Massell [67] attacked the problem more scientifically. They were able to evaluate therapeutic results by measuring the patient's ability to walk on a level surface at a given rate until claudication developed. Using this test, they found that testosterone propionate in doses up to 150 mg. a week did not prevent intermittent claudication in the lower limbs of 6 patients with occlusive vascular disease.

Sirota [68] used desoxycorticosterone acetate in the treatment of thromboangiitis obliterans and arteriosclerosis obliterans. This form of therapy was used because of the possibility that the adrenal cortex hormone might change salt metabolism internally and produce an effect similar to that of the intravenous administration of hypertonic salt solution. It is also claimed by many investigators that both of these preparations will increase the volume and lower the viscosity of the blood. Twenty cases were studied, and the oscillometric index, surface temperature and subjective improvement were used as criteria of cure. The author considered the results encouraging. From a study of his cases, however, this conclusion does not seem justified. Some patients were objectively better but subjectively worse, and vice versa. Improvement was certainly less than that reported with most of the established methods of treatment now available.

Fatherree and Hurst [69] studied the effect of an insulin-free, deproteinated pancreatic extract on 15 patients suffering from intermittent claudication. Nine of these patients suffered from thromboangiitis obliterans. Injections of 3 to 5 cc. were given on alternate days, excepting to 1 patient, who received the solutions daily. After an injection the authors were unable to ascertain a remarkable change in the blood pressure, pulse rate or digital cutaneous temperature. Of the 9 patients with thromboangiitis obliterans, 7 were improved clinically and 2 were unimproved, as indicated by the claudication tests performed. Of the 6 patients with arteriosclerosis obliterans, none had an increase in claudication time. The authors finally concluded that the substance must be of value for some patients with intermittent claudication, but they were unable to predict which patient would benefit without a clinical trial.

Gorham and Climenko [70] made several laboratory and clinical studies on a new insulin-free, histamine-free pancreatic tissue extract. Surface temperature and

66. Walker, T. C.: Use of Testosterone Propionate and Estrogenic Substance in Treatment of Essential Hypertension, Angina Pectoris and Peripheral Vascular Disease, J. Clin. Endocrinol. **2**:560 (Sept.) 1942.

67. Beaser, S. B., and Massell, T. B.: Therapeutic Evaluation of Testosterone in Peripheral Vascular Disease, New England J. Med. **227**:43 (July 9) 1942.

68. Sirota, H. H.: Value of Desoxycorticosterone Acetate in the Treatment of Peripheral Vascular Disease, J. Clin. Endocrinol. **3**:141 (March) 1943.

69. Fatherree, T. J., and Hurst, C.: Intermittent Claudication: Its Treatment with an Insulin Free, Deproteinated Pancreatic Extract (Depropanex), Ann. Int. Med. **17**:325 (Aug.) 1942.

70. Gorham, L. W., and Climenko, D. R.: The Role of Insulin-Free, Histamine-Free Pancreatic Tissue Extract in the Treatment of Peripheral Arterial Disease, Am. Heart J. **25**:486 (April) 1943.

plethysmographic studies were performed on dogs after intravenous injections of this substance. A transitory fall in blood pressure was first noted, followed by evidence of vasodilatation lasting as long as fifty minutes. When the extract was administered intramuscularly, very little effect on blood pressure was noted, but there was some evidence of peripheral vasodilatation. In tests on an isolated smooth muscle in oxygenated Ringer-Locke solution, relaxation of the muscle was also noted on the addition of this pancreatic tissue extract. The preparation was then injected intramuscularly into 16 normal persons. A rise in cutaneous temperature and an increase in arm volume were noted in all the subjects studied. When the opposite hand was placed in cold water for thirty seconds, far less vasoconstriction was noted after the tissue extract was used than in its absence. The substance was then injected into persons suffering from various types of peripheral vascular disorders, mainly vasospastic in origin. Similar results were obtained in almost all of them. Clinically 8 received complete symptomatic relief and 4 others received only partial relief.

Uttal [71] reports his impressions of Soap Lake (Washington) as a spa for the treatment of thromboangiitis obliterans. It differs little from that of other investigators who have studied this form of treatment. Uttal concludes that the Soap Lake water baths have neither a beneficial nor a harmful effect on the circulation in thromboangiitis obliterans. The only beneficial effect possible is due to the vasodilatation resulting from the temperature of the water (100 F.). Externally Soap Lake water causes second degree burns of the skin if applied in full concentration for too long a time. Internally the water causes a hemorrhagic gastroenteritis if taken by mouth in doses over the amount necessary to produce a mild laxative or purgative effect. The climatology and open outdoor life are beneficial to patients with this disease, and it is inexpensive to live in the town of Soap Lake. Uttal finally concludes that these factors definitely helped the patients psychologically, but in no other manner.

The successful management of 30 patients with night cramps is reported by Gootnick.[72] These patients were all veterans of World War I and were in the fourth or fifth decade of life. They suffered from various diseases, mainly arthritic. Evidence of peripheral vascular insufficiency could not be found. Gootnick is of the opinion that the pain was due to a lasting tetanic contraction of a muscle group secondary to a reflex stimulation from a neighboring focus of irritation. This focus could well be an arthritic joint, sciatic neuritis, a traumatic residuum or some other neighboring diseased area. In addition, muscles are more likely to be overstretched while a person is lying down, which results in a tendency to recoil into spasm. Blood calcium and phosphorus were found to be within the normal limits. Twenty-eight of the patients were afforded immediate relief after an evening dose of 3 grains (0.19 Gm.) of quinine sulfate. The other 2 patients received only partial alleviation. After administration of the drug was discontinued, 6 had an immediate recurrence and 10 had a recurrence within three days. By resuming use of the drug relief was again obtained.

An excellent review on the effects of radiation on the cardiovascular system has been compiled by Warren.[73] In this review he covers the literature on the effect of radiation on the normal heart and blood vessels.

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71. Uttal, J.: Soap Lake Water for Treatment of Thromboangiitis Obliterans, Northwest Med. **42**:99 (April) 1943.

72. Gootnick, A.: Night Cramps and Quinine, Arch. Int. Med. **71**:555 (April) 1943.

73. Warren, S.: Effects of Radiation on Normal Tissues: VI. Effects of Radiation on the Cardiovascular System, Arch. Path. **34**:1070 (Dec.) 1942.

Linton [74] was successful in preventing gangrene in a woman 58 years of age in whom the arterial blood supply to the left leg was interrupted by ligation of the hypogastric artery and occlusion of the external iliac artery secondary to trauma. Adequate arterial circulation was reestablished by means of intermittent venous occlusion. Long periods of occlusion and short periods of release were used.

Schaefer and Sanders [75] describe a case of temporal arteritis which responded to the oscillating bed when other methods for the relief of pain had failed.

A case of periarteritis nodosa apparently cured with sulfapyridine is reported by Goldman and his colleagues.[76]

By the local application of blood or concentrated plasma, Naide [77] was able to relieve pain quickly, reduce the inflammatory reaction and heal 9 of 15 chronic ulcers of the leg that had resisted previous treatment by other methods. Ten of the ulcers were on an ischemic basis due to arteriosclerosis or thromboangiitis obliterans, and the remaining 5 were of varicose origin. Although the mechanism of action is unknown, the question arises as to whether the applied blood supplies nutrition or whether by its sealing the ulcers with a crust of blood a more rapid healing process is initiated.

ARTERIAL HYPERTENSION

While the problem of essential hypertension is far from solution, a good deal has been done during the last year to clarify the subject and to erase earlier misconceptions in regard to its pathogenesis. Scott [78] still maintains that arteriosclerosis and arteriolosclerosis of the renal vessels constitute the essential pathologic defect which is responsible for the development of hypertension. He states that there is no evidence that disease of either the central nervous system or the vegetative nervous system may be the cause of this disorder. He appreciates the fact that there are other causes of hypertension than diseases of the kidney, and he emphasizes that an elevation of systolic pressure such as is usually found in elderly people may be persistently well above the normal without increasing the elevation of the diastolic pressure. This, of course, is essentially an atherosclerotic disease of the large elastic-coated blood vessels. He still maintains that the phenomenon of hypertension as reproduced in animals in which the main renal arteries are constricted is the exact counterpart of human benign essential hypertension, and he reminds the reader that even the clinical picture of malignant hypertension has been produced in animals by further narrowing of the renal arteries. He suggests also that the failure to find evidence of renal arteriosclerosis in many instances of human hypertension may well be due to the fact that sclerotic narrowing or other obstruction to vessels proximal to the kidneys is the essential factor. According to his conception, arteriosclerosis in one form or another, and in one location or another, is the primary disease of which hypertension is the manifestation. This process when affecting the vascular system of the kidneys excites the humoral mechanism which produces widespread vasoconstriction, and thus causes hypertension. Whether this is of the benign or the malignant type depends on the severity of the vascular lesion in the kidney.

74. Linton, R. R.: Treatment of Acute Arterial Occlusion by Means of Intermittent Venous Occlusion: Report of a Case, Arch. Surg. **46**:395 (March) 1943.

75. Schaefer, C. L., and Sanders, C. E.: Temporal Arteritis, Am. Heart J. **24**:410 (Sept.) 1942.

76. Goldman, B. A.; Dickens, K. L., and Schenken, J. R.: Apparent Cure of Periarteritis Nodosa with Sulfapyridine: Report of a Case, Am. J. M. Sc. **204**:443 (Sept.) 1942.

77. Naide, M.: Treatment of Leg Ulcers with Blood and Concentrated Plasma, Am. J. M. Sc. **205**:489 (April) 1943.

78. Scott, R. W.: Arterial Hypertension, J. A. M. A. **120**:1 (Sept. 5) 1942.

Schroeder [79] amplifies this view and states that arterial hypertension is characterized by increased peripheral resistance, owing to the presence of circulating pressor substances in the blood. These substances are released by the ischemic kidneys. They cause changes not only in the arterioles but in the hemodynamics of the kidneys, leading to permanent arteriolar change. His views differ from those of Scott in that he believes that functional spasmodic constriction of the arterioles by nervous or hormonal influence initiates the vicious circle which subsequently leads to organic changes in renal vessels. When some organic renal circulatory impairment is already present, hypertension may result from even a slightly intermittent increase in renal vasoconstrictor tone, whereas when the kidneys are entirely normal such activity perhaps induced through activity of the sympathetic nervous system may have no influence in affecting a rise in blood pressure. However, if such an increase in vasomotor activity occurs repeatedly and frequently, it may be sufficient in intensity to initiate a sequence of events which leads to the development of essential hypertension.

If the functional element acts alone, the course of the disease is likely to be prolonged. If there is an element of progressive structural damage and the functional one continues to exert an added influence, the course of the disease becomes more rapid and renal insufficiency may appear early. If both functional and structural elements progress rapidly, malignant hypertension is the result.

Page's [80] views stress the hormonal character of the pathogenesis of hypertension resulting from impairment of the blood flow through the kidney. He distinctly recognizes other types of increased blood pressure and is inclined to believe that functional vasomotor or neurogenic factors may initiate the renal ischemia which results in the release from the kidneys of the vasopressor substances responsible for subsequent rises in blood pressure. In this paper, he reviews particularly his own work and amplifies the evidence he has obtained in this work for these views in regard to the pathogenesis of hypertension. They are not new, and have been reviewed before. It is interesting to note, however, that he has found in a study of the cardiodynamic effects of angiotonin that they are practically identical to those observed in primary vascular hypertension as measured by the ballistocardiograph. The similarity of the tracings obtained on persons with hypertension and on persons whose blood pressure was normal but who were made hypertensive as a result of the administration of angiotonin are striking in their similarity. He emphasizes the fact that the heart is a part of the vascular mechanism and therefore may be expected to respond in much the same way that other parts of the vascular system react to pressor substances. His paper is simple and gives an easily understandable explanation of the essential mechanisms involved in the production of hypertension according to this theory.

Simonds [81] discusses the renal pathologic changes in hypertension and their clinical interpretation. He states that arteriolosclerosis with narrowing of the lumens of the afferent arterioles of the glomeruli is the pathologic equivalent of hypertension of long duration. In the first stage he concedes that there is probably a vasoconstriction involving these vessels which is not demonstrable as a structural change. He points out in this connection that the kidneys have both vasocon-

79. Schroeder, H. A.: Essential Hypertension: A Conception of Its Mechanism, Am. J. M. Sc. **204**:734 (Nov.) 1942.

80. Page, I. H.: Studies on the Mechanisms of Arterial Hypertension, J. A. M. A. **120**: 757 (Nov. 7) 1942.

81. Simonds, J. P.: Renal Pathogenic Changes in Hypertension and Glomerulonephritis: Clinical Interpretation, J. A. M. A. **120**:89 (Sept. 12) 1942.

strictor and vasodilator fibers. While there is little actual evidence that these have an active role in the control of renal function, the fact that there is a structural basis for sympathetic renal activity leads to the belief that it must become effective when the proper stimulus is applied. He also supports the theory of the vicious circle in hypertension. He states that "as long as the kidneys produce renin they remain ischemic, and as long as they remain ischemic, they continue to produce renin." Vasoconstrictor impulses of any type, regardless of their origin, may initiate this vicious circle. In the second and third stages arteriolosclerosis is not infrequent in many widespread locations in the body, but it is only in the kidneys that such changes have any constant association with hypertension. In the second stage, hypertrophy of the muscle coats and hyperplasia of the elastic laminas of the afferent arterioles are characteristic. In the third stage, the wall of the arterioles become transformed into hyaline tubes with narrowed lumens. In the two earlier stages the vessels are still capable of response to vasomotor stimuli, while in the final, or hyaline, stage such a response is no longer possible.

Chasis and Redish [82] have continued their important work on the function of the kidneys in hypertensive subjects and on renal blood flow. They believe that impairment of the renal parenchyma occurs early in hypertensive subjects and then proceeds in a parallel manner in the two kidneys. Apparently it does not follow the same pace in any two cases, but the decrease in blood flow in the two kidneys is practically the same. They failed to find a single instance of unilateral ischemia in 21 subjects with hypertension whom they had selected at random.

They also conclude that absolute reduction in renal blood flow in one or both kidneys as measured by the diodrast clearance does not necessarily indicate that renal ischemia is present. They state that such a conclusion can be drawn only if the blood flow for each unit of tubular excretory tissue can be evaluated.

They were unable to find any alteration in the patterns of the ureteropyelograms made on this group of patients. They further warn that excretory tests which compare the functions of the two kidneys must be evaluated with caution, because any variation in the quantity of urinary flow from these kidneys of itself may account for variations in the appearance time and relative concentration of the dye and even in the appearance of the shadows noted in excretory pyelography.

Castleman and Smithwick [83] studied the biopsy specimens obtained from the kidneys of 100 patients in the course of splanchnic resection for hypertension. The most striking result of these observations was finding such a high proportion of the renal biopsies in which there was no, or only minimal, degenerative disease in the vascular structures. Medial hypertrophy was present in only 40 per cent of the cases. Peripheral arteriosclerosis was present in only 7 per cent of the grade I group, whereas 60 per cent was noted with grades III and IV. Elevation of blood pressure precedes the development of structural disease of the blood vessels within the kidneys, as well as of the peripheral arterioles. It is therefore reasonable to believe that some vasoconstrictor mechanism carries on the ischemic process until renal vascular disease develops. When this has become established, hypertension becomes more severe, and the blood pressures of persons in that stage become fixed at higher levels.

82. Chasis, H., and Redish, J.: Function of the Separate Kidneys in Hypertensive Subjects, Arch. Int. Med. **70**:738 (Nov.) 1942.

83. Castleman, B., and Smithwick, R. H.: The Relation of Vascular Disease to the Hypertensive State Based on a Study of Renal Biopsy from One Hundred Hypertensive Patients, J. A. M. A. **121**:1256 (April 17) 1943.

Such results in the study of structural defects could well be expected under these conditions, for the patients in this group were no doubt selected for splanchnic section because little or no evidence of organic vascular disease could be detected.

It is also interesting to note that in this group adrenal tumors were found in 7 patients. The presence of the tumors was not suspected.

That hypertension is an important factor in the development of arteriosclerosis is indicated by the observations of Lake and his co-workers,[84] who found that there was a much higher incidence of this disease among persons with hypertension than in those without.

The factor of age is also emphasized by Russek [85] in discussion of the relationship of this factor to increased blood pressure. He found in a statistical analysis of blood pressure levels of 1,000 male subjects between the ages of 60 and 95 that there was an evident increase in the average systolic and pulse pressures with age. The diastolic pressure showed little variation after the age of 65. The incidence of normal blood pressure, of 150 systolic and 95 diastolic or less, decreased with age. Less than one half of the readings fell in this group. The incidence of normal systolic pressure increased with age, whereas that of normal diastolic pressure showed a tendency to fall with age. Arteriosclerosis apparently increased the incidence of systolic hypertension only. It is interesting to note that the life expectancy of the persons with systolic hypertension is of the same order as for those with normal pressure. Diastolic hypertension, on the other hand, carries a much less favorable prognosis. Diastolic hypertension was found in less than one-quarter of the entire group.

Howell [86] made essentially similar observations. He states that pronounced arteriosclerosis in the absence of systolic elevation in blood pressure was usually associated with poor physical condition, and he found the systolic blood pressure elevated in more than 42 per cent of his group of subjects.

Master [87] and his associates made another survey on 15,000 persons of all ages. The presence of hypertension in persons over 40 is becoming increasingly important because of the fact that many more persons survive this age. They gave further attention to the normal level of blood pressure, and in their paper they consider a fairly wide variation. The diastolic pressure was taken at the fifth phase, the disappearance of tone. They found very much the same increase in systolic pressure according to age among men. A majority showed an increase of pressure beginning with the age of 60, although this often occurred as early as the age of 50. At the age of 50 there were a 50 per cent incidence of hypertension in males and a 62 per cent incidence in females. The incidence of hypertension rose with each decade of age up through the eighth, and in the case of systolic pressure only, up through the ninth. The presence of some increase in blood pressure beyond the age of 40 is so common that in a mild degree it can no longer be considered abnormal, in their opinion.

Schroeder [88] studied 50 patients with early stages of hypertension. Thirty-five of these patients were under 30 years of age, and 15 were under 20. They apparently presented the earliest stages of the disease. Renal disease in some form was

84. Lake, M.; Pratt, G. H., and Wright, I. S.: Arteriosclerosis and Varicose Veins: Occupational Activities and Other Factors, J. A. M. A. **119**:696 (June 27) 1942.

85. Russek, H. I.: Blood Pressure in the Aged, Am. Heart J. **26**:11 (July) 1943.

86. Howell, T. H.: Blood Pressure and Old Age, Brit. Heart J. **4**:143 (Oct.) 1942.

87. Master, A. M.; Marks, H. H., and Dack, S.: Hypertension in People Over Forty, J. A. M. A. **121**:1251 (April 17) 1943.

88. Schroeder, H. A.: Studies on Essential Hypertension: IV. Early Arterial Hypertension, Am. J. M. Sc. **204**:62 (July) 1942.

present in 74 per cent, and Schroeder believes that this incidence was not a coincidence but rather an important factor in the genesis of the elevation of blood pressure. He thinks that organic vascular and renal diseases are thus intimately associated. Eleven of these patients were found to show dysfunctions of the nervous system, and every patient had abnormal nervous tension of some type. The onset of the increase of blood pressure in some cases was definitely associated with physical or psychologic disturbances.

The familial tendency to hypertension has long been a matter of discussion. Feldt and Wenstrand [89] in an analysis of 4,376 insurance examinations arrived at the conclusion that the incidence of familial cardiovascular disease was very slightly greater among hypertensive persons than it was among persons with normal blood pressure.

The psychosomatic aspects of hypertension are discussed by Weiss.[90] He states that two emotions are frequently closely related to hypertension. These are anxiety and rage. He emphasizes the fact that rage is an emotion which has long been connected with high blood pressure. In his opinion long-continued repressed rage may manifest itself through the circulatory system by elevation in blood pressure. Hypertension is one of the commonest disorders of civilized life, and anxiety states are no less common; therefore, from the standpoint of their frequency it is not surprising that the two are present often in the same person. It is his view that repressed rage results in a psychologic conflict which produces the tension which seems to be related to increased blood pressure, and that this is chief among multiple factors that enter into the pathogenesis of the disease. He emphasizes the fact that many of the symptoms of the hypertensive patient are not necessarily due to the increase in blood pressure but are due to the other associated disorders, both functional and physical. The emotional factors are as important as the physical factors. He stresses the frequent relationship of migraine to hypertension, and he believes that many of the severe headaches associated with hypertension may be on an emotional basis rather than due to any abnormality of blood pressure. All varieties of character and neurotic disturbances occur in hypertensive persons, but inhibited aggression seems to bear the most consistent relationship to this symptom, and this may well be one of the important factors initiating the development of the vasomotor disturbances of the primary phase of the disease.

In a discussion of the prognosis of hypertension a group of workers headed by Daley [91] classify the disorder in five major types: renal, endocrine and vascular hypertension; hypertension due to disease of the central nervous system, and the so-called essential hypertension, of unknown origin. They consider that blood pressures above 140 systolic and 90 diastolic are definitely abnormal at any age. The actual mortality exceeds the expected in a rapidly rising ratio for both systolic and diastolic values above this level. In the early stages of hypertension variability of blood pressure is well marked, but this initial variability is gradually succeeded by fixation at higher levels. This would indicate the development of organic changes in the arterioles in the form of hypertrophy of the media and arteriolosclerosis. The presence of atherosclerotic vascular changes superimposed on vasospastic diastolic hypertension is largely responsible for the mortality from this

89. Feldt, R. H., and Wenstrand, D. E. W.: The Family History in Arterial Hypertension: Studies of 4,376 Insurance Examinations, Am. J. M. Sc. **205**:61 (Jan.) 1943.

90. Weiss, E.: The Psychosomatic Aspects of Hypertension, J. A. M. A. **120**:1081 (Dec. 5) 1942.

91. Daley, R. M.; Ungerleider, H. E., and Gubner, R. S.: Prognosis in Hypertension, J. A. M. A. **121**:383 (Feb. 6) 1943.

disease. Thus, the duration of the presence of hypertension is also an important factor in prognosis. Cardiac enlargement and electrocardiographic as well as roentgen studies of the heart are valuable in estimating the outlook. Among patients with symptoms resulting from hypertension, a very large number showed electrocardiographic abnormalities. The status of the kidneys is also extremely important. The renal and urinary findings are usually sufficiently in evidence so that the diagnosis of malignant nephrosclerosis is at least suggested. There are many other factors to be considered in the outlook for this disease; the retinal findings are well known; the age at which hypertension develops seems to influence its course; the constitutional type of the hypertensive subject is another factor of importance. Sex is likewise a factor. While hypertension is more frequent in females, the course of the disease seems to be more benign than in males. Concurrent diseases such as diabetes constitute a factor of considerable importance in increasing the gravity of the prognosis.

Seasonal fluctuations in normal blood pressure are discussed in a paper by Paul,[92] who made observations on 900 healthy young men. Little variation could be established. This may be because his observations were made on a group of relatively young persons.

The effect of toxemia of pregnancy and of pregnancy on the hypertensive state has been the subject of a number of papers, and both still continue to be considered of importance in this disorder.

Dexter, Weiss, Haynes and Sise[93] present a comprehensive review of this subject. They based their observations on 100 normal pregnant women, 100 patients with generalized edema without hypertension during pregnancy and 80 patients with hypertension during pregnancy. Several types of hypertension in pregnancy were noted. Six to 9 per cent of the normal women had either hypertension or albuminuria or both in the latter half of pregnancy but not in the first half. Twenty of 39 patients who had hypertension before pregnancy failed to have any further increase in blood pressure or albuminuria during pregnancy in spite of the fact that many of them showed generalized edema. In the remaining members of this group with hypertension preceding pregnancy, toxemia developed. The vascular syndrome which was thus superimposed on previously existing hypertension differed in no way from the preeclampsia and eclampsia which occurred in patients whose blood pressure was normal before pregnancy. A progressive rise in the blood to above the level existing before pregnancy presaged the development of toxemia of pregnancy. Elevation of blood pressure and albuminuria of themselves do not indicate that toxemia is present.

These observers regard toxemia of pregnancy as an acute vascular disease which closely resembles acute glomerulonephritis. Etiologically and pathologically the two diseases differ. The most important factors predisposing to the development of toxemia are hypertensive disease and generalized edema. Persons with low renal reserve or with hypertension in the malignant phase seem to be especially susceptible.

Permanent vascular disease seems to follow toxemia of pregnancy much more frequently in those cases in which the duration of the disorder is prolonged and, curiously, in those cases in which the toxemia is mild rather than in those in which there is eclampsia. After a toxemic pregnancy, it is usual for hypertension to disappear rapidly. In some cases it may persist for a rather long time and even

92. Paul, H.: Seasonal Changes in Circulatory Factors, Arch. f. Kreislaufforsch. **9**:164 (Oct.) 1941.

93. Dexter, L.; Weiss, S.; Haynes, F. W., and Sise, H. S.: Hypertensive Toxemia of Pregnancy: Pre-Eclampsia and Eclampsia, J. A. M. A. **122**:145 (May 15) 1943.

then disappear permanently. It is impossible to differentiate such cases from those in which the hypertension is progressive and the condition becomes indistinguishable from other types of chronic hypertensive disease.

Tillman [94] comments on the difficulty of accepting the view that the eclampsia in pregnancy is the same as that in acute glomerulonephritis, even though the clinical pictures of the two disorders are similar. In the main, his conclusions are similar to those of the previous observers. Development of sudden severe hypertension during the course of pregnancy or sudden increase in blood pressure in preexisting hypertension is of the utmost significance. The ultimate outcome cannot be determined until after delivery. In many women the condition disappears at the time; in others persistent hypertension may follow, and a considerable number of the patients present themselves later in life with typical hypertensive vascular diseases.

Eastman and Whitridge [95] are more specific in their views in regard to a significant rise in blood pressure as an indication of impending eclampsia. They regard a rise from 110 systolic and 70 diastolic to 135 systolic and 85 diastolic in a young woman as of more significance than a rise from 135 systolic and 85 diastolic to 150 systolic and 90 diastolic in a patient of 35. They point out that in the person with hypertension each subsequent pregnancy adds its increment to its severity. Very often in such women the disease becomes progressive and pursues a malignant course. They state that chronic hypertension is superseding eclampsia as a cause of death in child bearing and that it has been responsible for 80 per cent of the toxemic deaths in their experience.

It is interesting to note that in rats previously made hypertensive by constriction of one renal artery the systolic pressure was reduced significantly during pregnancy. After delivery the pressure rose again to approximately the same level as before. This occurred if renal damage was not severe enough to impair function.[96]

Dalton and Nuzum [97] made statistical studies on patients with essential hypertension. It has been the opinion of most observers that renal function is not impaired in this disorder, but these observations would indicate otherwise. They were based on the urea clearance test and the excretion of phenolsulfonphthalein. Dalton and Nuzum state that in subjects with essential hypertension here is a significant reduction in the ability of the kidneys to concentrate urine and to excrete phenolsulfonphthalein. This reduction can be demonstrated only when the study is considered for entire groups of normal persons and of patients with hypertension. It cannot be shown when individual comparisons are made. The age of the patient and the duration of the disease seem to have little effect on renal function of either normal persons or patients with hypertension. An increase in the severity of the disease, that is, a rise in the diastolic blood pressure, is accompanied by reduction of renal function.

Studies of the adrenal glands were made by Dempsey [98] on patients with essential hypertension and on a group of persons with normal blood pressure. This pathologic study showed that the average weight of the adrenal glands of

94. Tillman, A. J. B.: Classification and Medical Relationships of Hypertensive Albuminuric Pregnancy, J. A. M. A. **120**:587 (Oct. 24) 1942.

95. Eastman, N. J., and Whitridge, J., Jr.: The Prevention of Toxemia of Pregnancy, J. A. M. A. **120**:729 (Nov. 7) 1942.

96. Foà, P. P.; Foà, N. L., and Peet, M. M.: Effect of Pregnancy on Experimental Renal Hypertension in Rats, Am. J. M. Sc. **204**:350 (Sept.) 1942.

97. Dalton, J. W., and Nuzum, F. R.: Critical Statistical Analysis of Data on Renal Function in Grouped Subjects with Essential Hypertension, Arch. Int. Med. **70**:948 (Dec.) 1942.

98. Dempsey, W. S.: The Adrenal Cortex in Essential Hypertension, Arch. Path. **34**: 1031 (Dec.) 1942.

subjects with hypertension was not significantly higher than in nonhypertensive persons. Adenomatous hyperplasia of the adrenal cortex was not found in association with essential hypertension, but it occurred with considerable frequency in nonhypertensive persons. The microscopic appearance of tortuosity of the adrenal cortical cords and abnormal deposition of fine lipid droplets in the cortical cells could not be associated with the gross findings of irregularity of the cords in the adrenal cortex.

Van Bogaert and van Baarle [99] state that in some cases of essential hypertension there are certain signs which resemble those produced by experimental stimulation of the hypothalamus in dogs. They were able to show the presence of hypophysial hormones in a larger than normal quantity in the body fluids, but they concluded that this does not necessarily indicate a causal connection between the hormones and increased blood pressures and that both the rise in blood pressure and these increased secretions are the result of stimulation of the encephalobulbar centers. The hypothalamus is among these.

Evans and Stewart [100] studied the peripheral blood flow before and after operation for adrenal pheochromocytoma. Several interesting observations are recorded. A decrease of peripheral blood flow was noted before operation. This was attributed to hyperepinephrinemia. The circulation time was shorter before operation than after. Low cutaneous temperatures and high rectal temperatures were noted before operation and were interpreted as being brought about by decreased peripheral blood flow and vasoconstriction, which result in increased heat storage. The periods of marked sweating which were observed suggested an attempt on the part of the organism to increase loss of heat from the body by the cooling effect of evaporation.

CLINICAL COUNTERPARTS OF EXPERIMENTAL HYPERTENSION

Aneurysm of the abdominal aorta is capable of causing renal ischemia of suffcient degree to produce hypertension of a fairly severe grade. This is indicated by a case reported by Hoffman.[101] The disease process in this case was a saccular aneurysm of the abdominal aorta in a Negro man aged 28. This aneurysm was in such a location that severe compression of one renal artery occurred. It was a typical clinical example of compression of the Goldblatt type. The outstanding change seen in the involved kidney was uniform and difuse atrophy of the nephron units with marked dilatation and engorgement of the glomerular and interstitial capillaries with red cells. There was apparently little or no sclerosis of the arterioles.

Another instance of hypertension [102] suspected to be the result of renal ischemia is reported as a complication of a dissecting aneurysm of the abdominal aorta. The blood pressure in this case was high, and the renal function was good. An intravenous urogram showed impaired excretion by the left kidney, but a retrograde pyelogram was normal. The dissecting aneurysm at autopsy had resulted in a complete occlusion of the left renal artery, while that of the right kidney was normal In this case, too, there was a striking absence of sclerosis or necrosis of the arterioles of the kidney.

99. van Bogaert, A., and van Baarle, F.: Contributions to the Study of Arterial Hypertension in Connection with the Hypothalamohypophysial System, Cardiologia **5**:275, 1941.

100. Evans, W. F., and Stewart, H. J.: Peripheral Blood Flow in the Case of Adrenal Pheochromocytoma Before and After Operation, Am. Heart J. **24**:835 (Dec.) 1942.

101. Hoffman, B. J.: Renal Ischemia Produced by the Abdominal Aorta, J. A. M. A. **120**: 1028 (Nov. 28) 1942.

102. Baerøe, K.: Hypertension as a Result of Renal Ischemia in Dissecting Aneurysm of the Aorta, Nord. med. (Norsk mag. f. lægevidensk.) **12**:3408 (Nov. 29) 1941.

That interference with blood flow through the renal arteries may be effected by so simple a lesion as torsion resulting from ptosis is shown by the case reported by Riskind and Greene.[103] The patient had a well marked hypertension. There was no demonstrable impairment of the function of either kidney. Torsion of the right kidney was suggested by urography. After the application of a corset by which correction of the torsion was made, the blood pressure fell, and it had remained "fairly close to normal." After removal of the support, the pressure rose again. The authors do not clearly state the findings after the support was applied, but apparently the result was definite improvement.

Richardson[104] found 25 instances of atherosclerosis of the renal arteries. In 22 of them the plaques were confined to a significant part of each artery near the aorta. In 2 the involvement was confined to one renal artery. In 8 there was a generalized atherosclerosis. In 12 atheroma was limited to the aorta, and in 5 no atheroma was discovered. Among the group there were 3 cases of malignant hypertension. Richardson believes that atheromatous plaques may be capable of producing renal ischemia and consequently hypertension analogous to experimental hypertension.

EXPERIMENTAL HYPERTENSION

Abell and Page[105] have continued to make direct observations on the blood vessels, particularly the arterioles, in the ears of rabbits. Experimental renal hypertension causes constriction in these vessels which is easy to see and which is persistent. It is not great enough to restrict the flow of blood to the tissues but is sufficient to produce increased peripheral resistance. This effect is produced even in the absence of nerve supply to the blood vessels, and therefore it must be due to the direct action of some substance on the vessel structures themselves. New arteriovenous anastomoses are formed. These observations are remarkably similar to those made when angiotonin is injected into the animal and hypertension produced in that manner.

That renal blood flow can be altered by the position of the kidney and the angle of the renal artery in relation to the aorta is shown by the experimental work of Gabriele.[106] His observations indicate that flow is reduced to a considerable degree when the angle is made relatively acute. Whether this is a factor in human hypertension depends on the mobility of the kidney. He considers it likely that the hypertension of pregnancy may be influenced by such a change in the position of the kidney.

The arterial hypertension which occurs in hydronephrosis has been the subject of experimental study by Megibow, Katz and Rodbard.[107] It was found that hydronephrosis produced by constriction or obstruction of the ureters of dogs resulted in elevation of blood pressure which was transient unless bilateral ureteral obstruction was complete. Under this condition hypertension existed until death of the animals in uremia. If the hydronephrosis was complicated by renal ischemia in one kidney the tendency to hypertension was increased. The authors believe that renal

103. Riskind, L. A., and Greene, H. H.: Renal Torsion and Ischemia Causing Hypertension, J. A. M. A. **119**:1016 (July 25) 1942.

104. Richardson, G. O.: Atherosclerosis of the Main Renal Artery in Essential Hypertension, J. Path. & Bact. **55**:33 (Jan.) 1942.

105. Abell, R. G., and Page, I. H.: The Effects of Renal Hypertension on the Vessels of the Ears of Rabbits, J. Exper. Med. **75**:673 (June) 1942.

106. Gabriele, D. J.: Effect of Kidney Position on Renal Blood Flow and Function, Am. J. M. Sc. **204**:227 (Aug.) 1942.

107. Megibow, R. S.; Katz, L. N., and Rodbard, S.: The Mechanism of Arterial Hypertension in Experimental Hydronephrosis, Am. J. M. Sc. **204**:340 (Sept.) 1942.

hypertension depends on the ratio of ischemic tissue to normal kidney tissue. Both factors operate in hydronephrosis, and the severity of the increase in blood pressure depends on the rapidity with which these processes develop. A compensatory increase in normal renal tissue may be the reason why the hypertension is transitory in those instances in which the obstruction to the ureter is not complete.

The renal lesions which seem to be most effective in the production of hypertension are those which interfere with the propagation of the arterial impulse through the vessels of the kidneys. These are ureteral obstruction, constricting perinephritis and inflammatory diseases. Pyelonephritis, hydronephrosis, tuberculosis and tumor are listed as common causes by White, Durkee and Mirabile.[108]

The part that renin plays in the production of the pressor substance which is responsible for the maintenance of elevation of blood pressure is so generally accepted that further review is not needed. It is the common opinion that renin is released only by impaired renal tissue. That the intact kidney may secrete renin under certain conditions is pointed out by Huidobro and Braun-Menendez.[109] They found that profound lowering of blood pressure by hemorrhage or shock causes liberation of renin by the intact kidneys of anesthetized dogs. They could detect the presence of renin in the blood of such animals, but if the kidneys had previously been removed none could be demonstrated under similar conditions. Nor could renin be detected in normal dogs when they were intoxicated with potassium cyanide or when they were made to breathe an atmosphere poor in oxygen. These authors believe that the renal humoral pressor mechanism participates in the normal maintenance of arterial blood pressure. When the blood pressure decreases sufficiently, renin is released, and this, through the formation of the pressor substance, helps to bring about a restoration of pressure to normal.

Weinstein and his associates[110] found that blood from a kidney in which the arterial blood flow and pressure had been greatly reduced possessed a greater vasoconstrictor effect and a lesser ability to neutralize angiotonin than did blood from a normal kidney.

Acute neurogenic hypertension produced by section of the moderator nerves[111] occurs even after both kidneys have been removed. The rise in arterial pressure occurs immediately under these conditions just as it does when the kidneys are intact in the animal. Thus it would seem that humoral pressor substances have no part in the mechanism of this type of experimental hypertension.

The rat has been found to be an animal suitable for the study of experimental hypertension, and it is being widely used for this purpose. Chronic hypertension can be produced by a variety of measures, according to Grollman and Williams.[112] They have found that the application of silk to the kidneys is an easy and practical procedure with relatively low operative mortality which results in permanent elevation of blood pressure.

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108. White, B. V.; Durkee, R. E., and Mirabile, C.: Renal Hypertension: A Review of Its Status Including a Report of a Case of Hypertension Relieved After Nephrectomy, New England J. Med. **288**:277 (March 4) 1943.

109. Huidobro, F., and Braun-Menendez, E.: The Secretion of Renin by the Intact Kidney, Am. J. Physiol. **137**:47 (Aug.) 1942.

110. Weinstein, H.; Friedman, M.; Newman, H. L., and Sugarman, J.: The Vasoconstrictor and Angiotonin Neutralizing Properties of Renal Venous Plasma, Am. Heart J. **25**: 682 (May) 1943.

111. Thomas, C. B.: Experimental Hypertension from Section of the Moderator Nerves: Relationship to the Presence of Kidney Tissue, Proc. Soc. Exper. Biol. & Med. **48**:24 (Oct.) 1941.

112. Grollman, A., and Williams, J. R., Jr.: Experimental Hypertension in the Rat, Am. J. M. Sc. **204**:73 (July) 1942.

Similar observations have been recorded by others,[113] with the same conclusions. The rat apparently has a predisposition to hypertension, so that the procedure is uniformly successful. Suitable methods for determining pressure have been devised.

As a consequence of the development of these methods of study, naturally a large number of reports have appeared on the effects of various and varied substances on the blood pressure of rats. Many of these are routine experiments with the common vasodilators. It is not possible to evaluate these results or their importance,[114] but it seems probable that experimentation in this field of therapeutics may prove to be extremely fruitful.

STUDIES OF DIODRAST AND OF INULIN CLEARANCE

The opinions in regard to the significance of determinations of diodrast and of inulin clearance as measures of the effective renal blood flow and the glomerular filtration rate are not entirely in agreement even after several years of observation, particularly when these measures are applied to the kidneys of hypertensive patients. The essential difference of opinion seems to be in regard to the detection of renal ischemia.[115]

Findley, Edwards, Clinton and White found that a high percentage of their relatively small group of patients with hypertension had normal clearance of diodrast and normal tubular excretion. Although no proof is at hand, they are inclined to believe, as Kohlstaedt and Page [116] do, that the production of the pressor substance resulting from the release of renin by the kidney is not dependent necessarily on actual reduction of renal blood flow but is due to the impairment of the pulsatile type of flow, with a reduction of pulse pressure within the renal vessels.

This opinion is shared by Foà, Woods, Peet and Foà,[117] who based their observations on studies of diodrast and of inulin clearance before and after surgical interruption of structures of the sympathetic nervous system according to the methods of Peet. These were carried out in cases of well advanced hypertension and in others in which the hypertension was not severe. Even though there was a reduction of blood

113. Schroeder, H. A.: Arterial Hypertension in Rats: I. Methods, J. Exper. Med. **75**: 513 (May) 1942.

114. Kempf, G. F., and Page, I. H.: Production of Experimental Hypertension and the Indirect Determination of Arterial Systolic Pressure in Rats, J. Lab. & Clin. Med. **27**:1192 (June) 1942. Duncan, G. W., and Hyman, C. M. S.: Determination of Blood Pressure in Rats by Direct Observation of Blood Vessels, ibid. **28**:886 (April) 1943. Rath, M., and Krantz, J. C.: Nitrites: X. Effect of Sodium Nitrite upon the Blood Pressure of Unanesthetized Hypertensive Rats, Proc. Soc. Exper. Biol. & Med. **50**:248 (June) 1942. Friedman, B.; Soloway, S.; Marrus, J., and Oppenheimer, B. S.: Quinones as Blood Pressure Reducing Agents in Hypertensive Rats, ibid. **51**:195 (Oct.) 1942. Calder, R. M.: Nutritional Deficiencies as a Cause of Elevated Blood Pressure in Rats, J. Exper. Med. **76**:1 (July) 1942. Grollman, A., and Harrison, T. R.: Reduction of Blood Pressure of Hypertensive Rats by Administration of Certain Marine Oils, Proc. Soc. Exper. Biol. & Med. **52**:162 (March) 1943. Oster, K. A., and Sobotka, H.: Antipressor Effects of Orthoquinoid Epinephrine Derivatives in Experimental Hypertension in the Rat, J. Pharmacol. & Exper. Therap. **78**:100 (May) 1943. Yeathem, J. H., and Drill, V. A.: The Effect of Diethylstilbestrol on the Blood Pressure of Normal and Hypophysectomized Rats, Am. J. Physiol. **139**:17 (May) 1943.

115. Findley, T.; Edwards, J. C.; Clinton, E., and White, H. L.: Clearance of Diodrast Phenolsulfonphthalein, and Inulin in Hypertension and in Nephritis, Arch. Int. Med. **70**:935 (Dec.) 1942.

116. Kohlstaedt, K. G., and Page, I. H.: Production of Renin by Constricting the Renal Artery of an Isolated Kidney Perfused with Blood, Proc. Soc. Exper. Biol. & Med. **43**:136 (Jan.) 1940.

117. Foà, P. P.; Woods, W. W.; Peet, M. M., and Foà, N. L.: Effective Renal Blood Flow, Glomerular Filtration Rate and Tubular Excretory Mass in Arterial Hypertension. Arch. Int. Med. **71**:357 (March) 1943.

pressure which was observed for as long as twelve months after operation, there was no significant change in the diodrast and on inulin clearance. Some factor other than renal ischemia is suggested as the primary cause of hypertension, and these observers expressed the opinion that intrarenal pulse pressure is the probable factor. They ascribe the effect of sympathectomy in lowering blood pressure to the removal of vasomotor tone from the arterioles of the kidneys, which may thus allow a greater pulse pressure. The reduction of systemic blood pressure occurs because less renin is secreted as a result of the increased pulsation within the kidneys. The amount of vasomotor relaxation which occurs is thought to be dependent on the amount of permanent organic change which has already occurred in the vessels affected. When this is minimal and vasoconstrictor tone maximum, good results may be secured. The converse is also true, and within the possible range all gradations may be present.

This hypothesis is ingenious and interesting and exceedingly plausible. The same question presents itself which has aroused controversy before: Do the vessels of the kidney regain their tone after denervation through increased susceptibility to humoral or hormonal substances, such as epinephrine?

RELATION OF UROLOGIC DEFECTS TO HYPERTENSION

It has been well established that there is a relationship between hypertension and some types of urologic disease, for example, chronic atrophic pyelonephritis, probably hydronephrosis and some types of tumor. It would seem that disease of the lower part of the urinary tract is not likely to cause a rise in blood pressure unless there is also some involvement of the vascular structure of the kidney. Studies of urologic defects and case reports continue to be frequent. Wosika, Jung and Maher [118] made a statistical study of a large group of cases, approximately 2,000. They found that 40 per cent of the patients with hypertension also had abnormalities of the urinary tract. Twenty-seven per cent of persons who had normal blood pressure also had urologic disease. These findings became more prominent with statistical analysis, so that the authors could conclude that the patient who has hypertension is more likely to have urologic defects than is the normal person.

A study of the retrograde pyelograms of 100 persons with hypertension and 100 without was made by Shrader, Young and Page.[119] Some variations in the form of the pyelogram seemed to be more common in persons who had hypertension. They had renal pelves which were larger than normal and pelves which were lower in position than usual. Other abnormalities, such as intrarenal pelvis, incomplete rotation, right-angled ureteropelvic juncture and bifid pelvis, were no more common than in normotensive persons. Twenty-two per cent of the patients who had defective pyelograms also had hypertension. The incidence of significant renal abnormalities in an unselected group of hypertensive patients was 19 per cent. The difference in the patterns of the pyelograms of persons with hypertension and of those without is not great enough to have any special significance.

Kahn and Laipply [120] found that in nearly all cases of hypertension which is persistent renal disease is bilateral. It is frequently more severe in one kidney

118. Wosika, P. H.; Jung, F. T., and Maher, C. C.: Urologic Hypertension as an Entity, Am. Heart J. **24**:483 (Oct.) 1942.

119. Shrader, J. C.; Young, J. M., and Page, I. H.: Pyelograms in Patients with Essential and Malignant Hypertension, Am. J. M. Sc. **205**:505 (April) 1943.

120. Kahn, J. R., and Laipply, T. C.: Frequency of Bilateral Renal Disease in Persons with Hypertension, Am. J. M. Sc. **203**:807 (June) 1942.

than in the other, often to the point of complete loss of function, but the other kidney is seldom normal. One thousand cases were included in this necropsy study. In all, the final diagnosis was arterial nephrosclerosis or arteriolar nephrosclerosis or both.

Flocks'[121] findings in a small group of cases carefully studied are similar but show a greater incidence of hypertension, probably because the renal defects were of types more likely to produce increased pressure. All his cases were instances of congenital hydronephrosis, infected hydronephrosis or renal calculus. In 23 of this group of 38 there was a consistent elevation of arterial tension.

Ratliff and Conger[122] are of the opinion that when hypertension is present in a person who has unilateral renal disease nephrectomy should be done, not only to cure the renal defect but because in a small proportion of such patients the hypertension will also be relieved. In 528 patients with hypertension the incidence of actual renal disease was small; in only 32 was there definite objective evidence. Of these, 12 had chronic pyelonephritis and 5 had calculi. The other patients did not have conditions of the type with which hypertension occurs.

That unilateral pyelonephritis can produce severe hypertension is substantiated by the case of a child of 12 years reported by Wilson and Chamberlain.[123] Nephrectomy resulted in a restoration of blood pressure to normal in spite of the fact that the patient showed evidence of extensive general vascular disease, evidently the result of the severe hypertension.

Braasch and Wood[124] comment on the incidence of hypertension and perinephritis. Of a group of 70 cases, in only 3 could there have been any relationship between the renal disease and the elevation of blood pressure. This is less than one-half the average incidence of hypertension.

The relationship of chronic pyelonephritis to hypertension is emphasized by the studies of Shure,[125] who in 11,898 autopsies found an incidence of 44.4 per cent, as compared with 34.9 per cent in a control group selected at random. This greater incidence occurred in cases of bilateral pyelonephritis. He found that when the disease was unilateral hypertension was comparatively rare. The incidence of hypertension increased with age and was parallel to the incidence of severe renal vascular damage.

Treatment of hypertension in the past two years has held considerable promise, but this has not yet been realized. The work done with renal antipressor substances as reported in last year's review has been advanced no further, although there is still hope that some help will come in the solution of this problem from the field of experimental study. Page[126] states that the "treatment of hypertension is still an experiment" and that impatience may lead only to forced conclusions rather than to the actual truth.

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121. Flocks, R. H.: Clinical Studies on the Relationship Between Renal Disease, Renal Function and Arterial Blood Pressure, J. Urol. **47**:602 (May) 1942.

122. Ratliff, R. K., and Conger, K. B.: Incidence of Renal Hypertension and of Cure by Nephrectomy, J. Urol. **48**:142 (Aug.) 1942.

123. Wilson, C. L., and Chamberlain, C. T.: Unilateral Renal Ischemia with Hypertension: Case Report, J. Urol. **47**:421 (April) 1942.

124. Braasch, W. F., and Wood, W. W., Jr.: Clinical Perinephritis and Its Effect on Blood Pressure, J. Urol. **48**:343 (Oct.) 1942.

125. Shure, N. M.: Pyelonephritis and Hypertension, Arch. Int. Med. **70**:284 (Aug.) 1942.

126. Page, I. H.: Medical Aspects of High Blood Pressure, J. Michigan M. Soc. **42**:294 (April) 1943.

Wakerlin and his associates [127] have continued their observations on the effect of hog renin in the treatment of experimental hypertension. They were able to prevent the development of experimental hypertension in dogs by daily intramuscular injections of partially purified hog renin for three months before and after the operation. Other similar organic preparations had no such effect. They were also able by daily injections of the same substance to produce striking reductions in the blood pressures of animals previously made hypertensive. Inactivated hog renin had had no effect on 1 of these animals when given previously. It is indeed curious that renin from dogs and from other animals prepared in a similar manner had no beneficial effect. The authors make no attempt to explain their results.

It was concluded by Schales, Stead and Warren [128] that the decrease in arterial pressure which they obtained in the treatment of clinical hypertension with renal extracts was nonspecific and had no definite effect on the humoral pressor mechanism. In their opinion the effect of the renal extracts which they prepared was related to the fever, sweating, weakness and severe local reactions produced by the administration of these substances.

Chasis, Goldring and Smith [129] also found that the blood pressure in subjects with hypertension can be reduced by artificial fever induced by intravenous injection of such substances as triple typhoid vaccine and pyrogenic inulin. The reduction in pressure could be maintained in some instances by repeated injection, and the same result could also be achieved when fever was prevented by the administration beforehand of aminopyrine.

They expressed the belief that the mechanism of this reduction is merely a depressing effect on the cardiovascular system and not due to any corrective influence on the mechanism of hypertension.

Friedman, Jarman and Marrus [130] came to a similar conclusion in regard to the fall in blood pressure which they observed after subcutaneous implantation of strips of tissue from the kidney, liver and spleen. The depressor effect seemed to be related to the presence of necrotic tissue.

Interest in the possible action of pressor amines, particularly the effect of tyrosinase [131] on them, has continued to arouse interest. Whether this is entirely a nonspecific effect, such as that following the injection of irritant extracts, remains

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127. Wakerlin, G. E.; Johnson, C. A.; Smith, E. L.; Gomberg, B.; Weir, J. R.; Moss, W. G., and Goldberg, M. L.: Treatment of Experimental Renal Hypertension with Partially Purified Renin, Am. Heart J. **25**:1 (Jan.) 1943.

128. Schales, O.; Stead, E. A., and Warren, J. V.: Non-Specific Effects of Certain Kidney Extracts in Lowering Blood Pressure, Am. J. M. Sc. **204**:797 (Dec.) 1942.

129. Chasis, H.; Goldring, W., and Smith, H. W.: Reduction of Blood Pressure Associated with Pyrogenic Reaction in Hypertensive Subjects, J. Clin. Investigation **21**:369 (July) 1942.

130. Friedman, B.; Jarman, J., and Marrus, J.: Therapeutic Agents and Renal Implantation in Experimental Hypertension, J. Mt. Sinai Hosp. **8**:534 (Jan.-Feb.) 1942.

131. Soloway, S., and Oster, K. A.: Inactivation of Pressor Amines by Quinones and Related Diketones, Proc. Soc. Exper. Biol. & Med. **50**:108 (May) 1942. Alles, G. A.; Blohm, C. L., and Saunders, P. R.: Tyrosinase and Phenolic Pressor Amines, J. Biol. Chem. **144**:757 (Aug.) 1942. Schroeder, H. A.: Effect of Preparation of Amine Oxidase on Experimental Hypertension, Science **95**:306 (March 20) 1942. Oster, K. A., and Soloway, S.: Studies on the Oxidative Destruction of Pressor Amines, J. Mt. Sinai Hosp. **9**:160 (Sept.-Oct.) 1942.

to be secn. It is curious to note that heat-inactivated tyrosinase as employed by Prinzmetal [132] and his associates had a definite effect in lowering blood pressure, almost equal in fact to that following the use of the enzyme in the active state.

Goldblatt and his associates [133] have reviewed their work on application of a wide variety of therapeutic measures to experimental hypertension in dogs. This is a comprehensive and decisive discussion of the subject, but it is also pessimistic. They emphasize the value of studies of this kind in determining the results to be expected in human hypertension, but it is, of course, obvious that the fundamental differences between experimental hypertension in animals and the most common variety of arterial hypertension in man make comparison of therapeutic effects quite uncertain. The fundamental mechanism is no doubt similar but its application is too different to make the observations comparable for therapeutic use.

It seems safe to conclude that the status of medical treatment of hypertension remains unaltered. The use of the sulfocyanates continues to have its proponents and opponents.[134] The general opinion seems to be that these are the only drugs which have a specific effect in the reduction of blood pressure in the hypertensive state. That this effect can be obtained in experimental hypertension, even though only with an amount which produces toxic reactions, suggests that thiocyanate may have some influence on the humoral mechanism. It is not equally effective, clinically, in all cases. In many instances there is no response, and in some there is reported relief of subjective symptoms without reduction in pressure.

Other drugs, except for the group of sedatives, give little or no lasting benefit, and it has been pointed out again that much of the improvement reported in various medical treatments of this disorder is merely the natural variation of pressure which occurs so characteristically, often only an emotional response and vasomotor activity.[135]

A CRITICAL REVIEW OF THE LITERATURE ON VASCULAR SURGERY

Surgical thought this year is naturally focused on war injuries and their treatment. The present review deals with efforts to treat vascular lesions surgically; notable among these are the results obtained from ligation of the patent ductus arteriosus in the presence of subacute bacterial endocarditis.

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132. Prinzmetal, M.; Alles, G. A.; Margoles, C.; Kayland, S., and Davis, D. S.: Effects on Arterial Hypertension of Heat-Inactivated Tyrosinase Preparations, Proc. Soc. Exper. Biol. & Med. **50**:288 (June) 1942.

133. Goldblatt, H.; Kahn, J. R., and Lewis, H. A.: Studies on Experimental Hypertension: XVII. Experimental Observations on the Treatment of Hypertension, J. A. M. A. **119**:1192 (Aug. 8) 1942.

134. Caviness, V. S.; Umphlet, T. L., and Royster, C. L.: Blood Pressure and Sulfocyanates (Thiocyanate), Am. J. M. Sc. **204**:688 (Nov.) 1942. Moia, B., and Quesada, R.: Treatment of Arterial Hypertension by Thiocyanate, Rev. argent. de cardiol. **9**:41 (March-April) 1942. Tuckwiller, P. A.: The Use of the Thiocyanates in Hypertension, West Virginia M. J. **38**:235 (July) 1942. Goldsmith, G. A., and Cordill, S.: The Vasodilating Effects of Nicotinic Acid, Am. J. M. Sc. **205**:204 (Feb.) 1943. Cannady, E. W., and Allen, H. N.: The Treatment of Hypertension with Potassium Sulfocyanate, Illinois M. J. **82**:146 (Aug.) 1942. Quattlebaum, J. T.: Treatment of Hypertension: Thiocyanate in Normal Person, J. South Carolina M. A. **38**:112 (May) 1942. Russell, W. O., and Stahl, W. C.: Fatal Poisoning from Potassium Thiocyanate Treatment of Hypertension, J. A. M. A. **119**:1177 (Aug. 8) 1942. Flaxman, N.: Treatment of the Hypertensive Patient in the Precardiac Stage, Am. J. M. Sc. **205**:696 (May) 1943.

135. Allen, E. V.: Why Are so Many Preparations Said to Reduce Blood Pressure in Cases of Hypertension? Proc. Staff Meet., Mayo Clin. **17**:519 (Oct. 7) 1942.

VENOUS OCCLUSIONS

In 30 per cent of 280 autopsies considerable obstruction was found at the mouth of the left common iliac vein. This seems to be a developmental defect, but secondary, postnatal inflammatory reactions may aggravate it. This anatomic study throws an interesting light on the increased frequency of venous occlusions on the left side.[136]

Ligation of the femoral vein, devised as a prophylactic measure against pulmonary embolism when the origin of the thrombus is in the calf, continues to be in favor in properly selected cases. Patterson [137] reported the case of a critically ill sailor with osteomyelitis, thrombophlebitis and pulmonary embolism; after ligation of the femoral vein the patient had no more emboli and recovered. Moore [138] found that of the 39 living patients admitted to the Massachusetts General Hospital after the Cocoanut Grove disaster, 13 per cent presented thromboembolic phenomena; when he considered only the patients with third degree burns requiring a prolonged stay in the hospital, 4 of 9 patients had thrombosis of the veins of the leg. In their cases ligation of the femoral vein was done, below the deep femoral artery, unless the clot had extended past this level. No opaque material was injected in these cases to visualize the clot, since the venograms are often misleading and the procedure is irritating to the intima of the veins.

We have reported on these phlebograms in previous reviews; we thoroughly agree that the help obtained from them is not commensurate with the untoward reactions and the difficulty of interpretation. We do believe, however, in the use of anticoagulants after ligation of the femoral vein. According to the physicians specializing in vascular diseases at the Massachusetts General Hospital, neither heparin nor dicoumarin is useful, "since they only prevent further extension of thrombosis and, therefore, do not guard against fatal embolism."

Because the propagating thrombus, which may well occur proximally to the ligature or reside in the pelvic veins, is exactly the part of the thrombus most likely to break loose, the proper use of anticoagulants after operations on large veins has much to recommend it; it also inhibits the propagation of thrombi at the site of the pulmonary embolus, which is often recognizable clinically and at autopsy.

In 3 cases of septic pelvic phlebitis ligations of the ovarian vein and the vena cava were performed. All 3 patients showed a dramatic fall in temperature; all 3 recovered.[139]

ARTERIAL OCCLUSIONS

Individual reports of successful embolectomies continue to appear. Four cases were reported by Lesser.[140] The number of hours that elapsed between the onset of occlusion and the time of operation were four and a half, twelve, thirteen and fourteen. The attempt at conservative management should not be prolonged beyond six hours after the vascular accident. A riding embolus at the aortic bifurcation was removed at a laparotomy done with spinal anesthesia; the patient died on the

136. Krumbhaar, E. B., and Ehrich, W. E.: A Frequent Obstructive Anomaly of the Mouth of the Left Common Iliac Vein, Tr. A. Am. Physicians **57**:196, 1942.

137. Patterson, J. K.: Femoral Vein Ligation for Thrombophlebitis with Pulmonary Embolism, U. S. Nav. M. Bull. **41**:512 (March) 1943.

138. Moore, F. D.: A Note on the Thrombophlebitis Encountered, Ann. Surg. **117**:931 (June) 1943.

139. Collins, C. G.; Jones, J. R., and Nelson, E. W.: Surgical Treatment of Pelvic Thrombophlebitis, New Orleans M. & S. J. **95**:324 (Jan.) 1943.

140. Lesser, A.: Embolic Arterial Occlusion of Lower Extremities, J. A. M. A. **122**:285 (May 29) 1943.

twenty-seventh postoperative day from a pulmonary infarction.[141] In another case death occurred as a result of pulmonary embolism during the extraction of a clot from the common iliac artery; the fatal pulmonary embolus was caused by clots breaking loose from the right auricle of an old rheumatic heart.[142]

Murray [143] reported 5 aortic embolectomies done through an abdominal extraperitoneal approach. The circulation was restored in all 5 cases, and the impending gangrene of both legs in each case was immediately replaced by normal circulation in the extremities. While 4 of the patients sooner or later died of repeated visceral or cerebral emboli, the results are impressive. Certainly the therapeutic problem following embolectomy is the prevention of future emboli. The surgeon here must look for guidance to the internist, the pharmacologist and the biochemist. The present anticoagulants cannot be given for many months and years, and emboli can occur during administration of heparin, as in 2 of Murray's cases.

The response of individual patients to heparin varies a great deal; this observation led to the suggestion that the patient's tolerance to heparin might serve as a test of the clotting mechanism.[144] Patients during the first few days after major operations, following thrombosis of any kind and in acute stages of Buerger's disease exhibited resistance to heparin. The test helps to direct the proper dosage, especially when intermittent administration is used.

WAR INJURIES TO THE VASCULAR TREE AND THE VASOMOTOR SYSTEM

Neurologic, thoracic and orthopedic surgery have been developed to a much higher degree of efficiency in the surgical teaching centers than vascular surgery. Ligatures and sutures of lateral wounds of arteries offer more promise during circumstances prevailing in advanced hospitals than spectacular restorative sutures.[145] The problems involved in the treatment of traumatized blood vessels were concisely stated by Gage.[146] While men who have had unusual opportunity for practicing suture of blood vessels strongly advocate its use instead of ligatures,[147] most medical officers would find it more practicable or would be forced to use a ligature, protecting the limb with a block of the regional sympathetic nerve supply.[148] Articles adequately covering this field have been published by Pratt.[149] Holman [150] described concussion of an artery leading to segmental spasm, contusion of an artery leading to thrombosis and embolism, and lateral and circular wounds

141. Pearl, F. L.: Peripheral Embolism, with Report of Two Cases Successfully Treated by Femoral Embolectomy, in Medico-Surgical Tributes to Harold Brunn, Berkeley, Calif., University of California Press, 1942, p. 371.

142. Wikle, H. T., and Cabot, N.: Embolectomy for Riding Embolus of Abdominal Aorta, Surgery **13**:264 (Feb.) 1943.

143. Murray, G.: Aortic Embolectomy, Surg., Gynec. & Obst. **77**:157 (Aug.) 1943.

144. de Takáts, G.: Heparin Tolerance: A Test of the Clotting Mechanism, Surg., Gynec. & Obst. **77**:31 (July) 1943.

145. McNealy, R. W.: Blood Vessel Surgery in War, editorial, J. Internat. Coll. Surgeons **5**:363 (Sept.-Oct.) 1942.

146. Gage, M.: Traumatic Injuries to Peripheral Vessels in Both Civil and Military Practice, editorial, Surgery **11**:983 (June) 1942.

147. Goodman, C.: Blood Vessel Suture: Its Use Instead of the Ligature in War Surgery, Am. J. Surg. **60**:196 (May) 1943.

148. de Takáts, G.: Vascular Surgery in the War, War Med. **3**:291 (March) 1943. Pratt, G. H.: The Treatment of Traumatic and War Wounds of the Vascular System, Am. J. Surg. **57**:26 (July) 1942.

149. Pratt, G. H.: Surgical Management of Traumatic Lesions of the Arteries, S. Clin. North America **23**:358 (April) 1943.

150. Holman, E.: War Injuries to Arteries and Their Treatment, Surg., Gynec. & Obst. **75**:183 (Aug.) 1942.

of arteries. Ligation of the artery should always be followed by division. The treatment of arterial and arteriovenous aneurysms is discussed.

Blakemore and his associates[151] describe a significant set of experiments, in which vitallium tubes were used as a prosthesis to bridge arterial defects. The tube was lined with a segment of vein by a method requiring no sutures. These grafts were successful in contaminated wounds with the help of oral medication with sulfathiazole. The advances in the control of serious infections and the possible use of anticoagulants afford a real basis for success. The authors point out that if the anastomosis can remain patent for fourteen days when the post-traumatic edema subsides, the limb can be saved. Preserved veins for grafts are suggested.

Since the indications for amputation in war wounds are based mostly on the integrity of the main blood vessels, these contributions deserve a thorough clinical trial. While the results of experiments on animals are most encouraging, the single clinical case reported is not yet conclusive. The tubes are not widely available, and the method requires detailed study. Its use will be probably limited to special teams trained for this type of work.

The technical details contained in these articles on traumatic injuries to blood vessels are purposely omitted, since they are not within the scope of this journal.

The incidence of causalgic states, representing painful vasodilatation with edema, osteoporosis and spreading neuralgia, is increasing again. They most often follow partial injuries to nerves or injuries around small joints of the hand and foot. Early recognition and repeated procaine hydrochloride block of the regional sympathetic ganglions are recommended. When the condition progresses to a late stage it may gradually "burn out," leaving much deformity, or become intractable.[152]

The immersion foot syndrome following exposure to cold has been admirably studied by White,[153] who has summarized the previous observations. Survivors of torpedoed vessels have been exposed to cold air and water, prolonged dependency of the legs, malnutrition and vitamin deficiency. The process seems to differ only in degree of chilling and wetting from frostbite, trench foot and shelter foot. This ischemia during prolonged exposure to cold is followed by a period of active hyperemia which is mainly due to the clinical effects of the products of injury to the tissue. Paralysis of vasoconstrictor fibers is an added factor but seems of secondary importance.

In spite of the increased blood flow in the main vessels, the bounding pulse and the increased cutaneous temperature, the cutaneous capillary bed does not seem to receive adequate oxygen for its increased metabolic demand. Capillary permeability increases, and edema, pain and petechial hemorrhages occur. By cooling the skin, this disparity between supply and demand for blood is diminished.

The inflammatory reaction and hyperemia subside in a few weeks, and the circulation gradually returns to normal. Neuritic pain, however, makes its appearance when the injured nerves begin to regenerate. In the severe forms, this may

151. Blakemore, A. H.; Lord, J. W., Jr., and Stefko, P. L.: The Severed Primary Artery in the War Wounded, Surgery **12**:488 (Sept.) 1942; Restoration of Blood Flow in Damaged Arteries: Further Studies on a Nonsuture Method of Blood Vessel Anastomosis, Ann. Surg. **117**:481 (April) 1943.

152. Miller, D. S., and de Takáts, G.: Post Traumatic Dystrophy of the Extremities, Surg., Gynec. & Obst. **75**:558 (Nov.) 1942. de Takáts, G., and Miller, D. S.: Post Traumatic Dystrophy of the Extremities: Chronic Vasodilator Mechanism, Arch. Surg. **46**:469 (April) 1943.

153. White, J. C.: Vascular and Neurologic Lesions in Survivors of Shipwreck: I. Immersion Foot Syndrome Following Exposure to Cold, New England J. Med. **228**:213 (Feb. 18) 1943; II. Painful Swollen Feet Secondary to Prolonged Dehydration and Malnutrition, ibid. **228**:241 (Feb. 25) 1943.

persist for as long as six months. Suitable treatment, as suggested by Commander White, consists of first aid methods against general chilling but never heating the chilled extremity. The affected limb is to be kept cool, elevated and surgically clean. Pressure points on the feet, especially the heels, should be avoided. No rubbing or massage is permissible. For cooling of the limb, simple exposure to room air may suffice. An electric fan placed on a bed table may blow air over the feet; the patient may spray water from an atomizer into the stream of air flowing from the fan.

The naval medical officers at Halifax worked out a method of packing such extremities in ice, which is changed every four hours. The purpose of this pack is to cool the temperature of the skin to a level between 80 and 85 F. These packs have been kept on as long as eleven days.[154]

Buerger's exercises and possible sympathectomy for late stages of the immersion foot are suggested.

The study of another group of survivors reported by Ungley [155] makes it obvious that the vascular and neurologic lesions were greatly aggravated by rapid heating in front of the galley stoves of the trawlers which rescued them and had no medical officers.

It is interesting to note that survivors torpedoed in relatively warm water (around 70 F.) also show painful, swollen limbs, but these are predominantly due to dependency, immobility, hypoproteinemia from starvation and multiple vitamin deficiences. Commander White stressed the point that this syndrome is not identical with the immersion limb and that it calls for a high protein, high vitamin diet.[156]

It is to be expected that further clinical experience and possibly clinical investigations will clarify the optimal prophylaxis, first aid and hospital care of men exposed to freezing cold and chilled wet environment. This seems to be an important subject and has obviously received less study than burns have. Severe freezing of limbs of dogs may cause shock and death and may be prevented by immediate application of pressure dressings.[157] When the human hand is cooled by immersion in cold water (5 C.), the swelling may amount to 15 per cent of the original volume in three hours; the protein content of the edema-fluid is around 3 per cent.

The crushing injury to limbs which occurs in persons caught under a wreck and pinned there for several hours has a certain superficial similarity to immersion foot, since severe capillary damage and exudation of protein-rich edema fluid occur. Much experimental and clinical work has been done on this syndrome. It seems that approximately 5 per cent of air raid casualties in an urban area may be of this type. A total of 70 such cases have been reported to the British Medical Research Council. For treatment ample intake of alkaline fluids by mouth, plasma and blood for the shock and cooling of the limb with even elastic compression were recommended by Bywaters.[158] He has shown, with Popjak,[159] that in the rabbit

154. Webster, D. R.; Woolhouse, F. M., and Johnston, J. L.: Immersion Foot, J. Bone & Joint Surg. **24**:785 (Oct.) 1942.

155. Ungley, C. C., and Blackwood, W.: Peripheral Vasoneuropathy After Chilling: "Immersion Foot and Immersion Hand," with a Note on the Morbid Anatomy, Lancet **2**:447 (Oct. 17) 1942.

156. White.[153] Webster.[154] Ungley.[155]

157. Fell, E. H., and Hanselman, R.: Prevention of Shock and Death by Immediate Application of a Pressure Dressing to the Severely Frozen Limbs of Dogs. Ann. Surg. **117**: 686 (May) 1943.

158. Bywaters, E. G. L.: Crushing Injury, Brit. M. J. **2**:643 (Nov. 28) 1942.

159. Bywaters, E. G. L., and Popjak, G.: Experimental Crushing Injury: Peripheral Circulatory Collapse and Other Effects of Muscle Necrosis in Rabbit, Surg., Gynec. & Obst. **75**:612 (Nov.) 1942.

the human condition of the "crush syndrome" can be simulated with the exception that renal failure and myohemoglobinuria are absent, since rabbit muscle does not contain myohemoglobin. Bywaters and Duncan and Blalock [160] expressed the belief that the local loss of fluid into the crushed limb does not explain the entire clinical picture; the ultimate fatal outcome of long-lasting compressions was due mainly to absorption of toxic products.

The renal lesions occurring in the experimental animal have been studied by Eggleton and her associates.[161] Their observations indicate that the experimental lesions which have been produced by binding the hindlimbs of dogs tightly with rubber tubing and compressing the thigh muscles in a vise for five hours resulted in a picture identical with the clinical syndrome. Severe oliguria with appearance of pigmented urine and a low creatinine clearance occurs. Anuria may follow. The renal damage seems to be in the terminal portion of the proximal convoluted tubules. Their evidence suggests that the main factor in the crush syndrome—after plasma has been restored—is an increased permeability of the renal tubules due to a toxic agent released from the damaged limbs. Certain substances, such as uric acid and phosphoric acid, are known to have a selective action on tubular segments, where the reaction of the urine changes. Such renal changes in men were seen in 2 cases of crush syndrome by Dunn and his associates.[162]

This subject is reviewed here because it revives the toxemic theory of shock, which after the last war became relegated to the background in face of the great interest in the local loss of plasma and its deleterious effect on blood volume and general capillary permeability. The toxic component in this syndrome has been acknowledged by such an authority on shock as Blalock.[160] The syndrome is also interesting because it may occur after acute occlusion and release of a main artery. In a case of a central dislocation of the hip with fracture of the pubic rami, the iliac vessels were obstructed by pressure against the inguinal ligament. Relief of the obstruction by dividing Poupart's ligament was followed by sudden collapse. Death occurred four days later from uremia. The limb became very hard after the release, but circulation remained restored. The kidney showed tubular degeneration and blood in the tubules. The blood urea content rose to 200 mg. per hundred cubic centimeters.[163]

Surgeons are well aware that somnolence, "toxic psychosis" and a gradual rise in the nonprotein nitrogen content of the blood not infrequently occur in patients with gangrenous extremities, which may rapidly clear up after amputation.

VASCULAR ANOMALIES AND ANEURYSMS

Hemangiomas are inherited as an autosomal dominant from a presumably homozygous man.[164] Their treatment, especially if surgical incision is too deform-

160. Duncan, G. W., and Blalock, A.: The Uniform Production of Experimental Shock by Crush Injury: Possible Relationship to Clinical Crush Syndrome, Ann. Surg. **115**:684 (April) 1942; Shock Produced by Crush Injury: Effects of the Administration of Plasma and the Local Application of Cold, Arch. Surg. **45**:183 (Aug.) 1942.

161. Eggleton, M. G.; Richardson, K. C.; Schild, H. O., and Winton, F. R.: Renal Impairment Due to Crushing Limbs in Anesthetized Dogs, Brit. M. J. **2**:392 (Oct. 3) 1942.

162. Dunn, J. S.; Gillespie, M., and Niven, J. S. F.: Renal Lesions in Two Cases of Crush Syndrome, Lancet **2**:549 (Nov. 8) 1941.

163. Glen, A. M.: Temporary Vascular Occlusion Ending Fatally in Uremia, Brit. M. J. **2**:875 (Dec. 20) 1941.

164. Beers, C. V., and Clark, L. A.: Tumors and Short-Toe—Dihybrid Pedigree: Family History Showing Inheritance of Hemangioma and Metatarsus Atavicus, J. Hered. **33**:366 (Oct.) 1942.

ing or impossible, is preferably by the use of implanted radon seeds (Johnson [165]; Byars [166]). In a case of cirsoid aneurysm of the scalp, Patey [167] used a combination of arterial ligatures (both external carotid arteries) and sclerosing injections into the dilated vascular trunks. The lesion was cured.

Henry gives an excellent historical review of the evolution of surgical treatment of aneurysms.[168] Three cases of traumatic arteriovenous fistula of the common femoral vessels are reported,[169] in which venography located the level of the fistula. The vein distal to the fistula was always normal, in contrast to the segment proximal to it. Ligation of the vein distal to the fistula appeared to have the same beneficial effect on the extremity that ligation of the vein proximal to the fistula has on the heart.

For an aneurysm of the right subclavian artery Wheeler [170] divided a portion of the sternum and retracted it upward with the inner end of the clavicle. He then tied the innominate artery. The patient lived eight years after the operation and then died presumably from a rupture of the aneurysmal sac. An arteriovenous aneurysm involving the left innominate vein and the left common carotid artery was successfully closed by obliterating the sac with three arterial clamps, which the authors were forced to place and leave in situ for twelve to fourteen days. One postoperative hemorrhage occurred a month later, but the patient got completely well and works in a munitions factory, lifting 75 to 100 pound (35 to 45 Kg.) weights.[171]

THE VASOMOTOR APPARATUS

Learmonth and Richards [172] did an anterior root section from the fifth cervical to the second dorsal segment for athetosis of the right arm. Observations with reflex vasodilatation showed that this extremity responded well, even though the most cranial source of its preganglionic vasoconstrictor fibers was the third thoracic segment.

Vasodilatation after sympathetic block is purely a release from vasoconstriction, but the muscles of the forearm do not participate in the vasodilatation.[173]

Hinsey and his co-workers [174] believe to have shown that after preganglionic sympathectomy in cats a functional reorganization of sympathetic ganglions can

165. Johnson, G. S., and Light, R. A.: The Treatment of Congenital Hemangiomata of the Skin, Ann. Surg. **117**:134 (Jan.) 1943.

166. Byars, L. T.: The "Malignant" Hemangioma, Surg., Gynec. & Obst. **77**:193 (Aug.) 1943.

167. Patey, D. H.: A Case of Arteriovenous (Cirsoid) Aneurysm of the Scalp, Successfully Treated by Combined Arterial Ligation and Venous Injection, Brit. J. Surg. **29**:290 (Jan.) 1942.

168. Henry, A. K.: Some Surgical Aspects of Aneurysm, Practitioner **150**:136 (March) 1943.

169. Watson, J. R.; Lichty, J. M.; Hill, J. M., and Miller, R. B.: The Use of Venograms for the Localization and Study of Arteriovenous Fistula, Surg., Gynec. & Obst. **76**:659 (June) 1943.

170. Wheeler, W. I. de C.: Ligature of Innominate Artery for Right Subclavian Aneurysm: End Result, Brit. M. J. **2**:422 (Oct. 10) 1942.

171. Tarnower, H.; Lattin, B., and Adie, G. C.: Successful Closure of an Arteriovenous Aneurysm Involving the Left Innominate Vein and the Left Common Carotid Artery, Ann. Surg. **116**:700 (Nov.) 1942.

172. Learmonth, J. R., and Richards, R. L.: Note on the Spinal Origin of Vasoconstrictor Fibers to Arm in Man, Quart. J. Exper. Physiol. **32**:87 (May) 1943.

173. Warren, J. V.; Walter, C. W.; Romano, J., and Stead, E. A., Jr.: Blood Flow in the Hand and Forearm After Paravertebral Block of the Sympathetic Ganglia: Evidence Against Sympathetic Vasodilator Nerves in the Extremities of Man, J. Clin. Investigation **21**:685 (Nov.) 1942.

174. Hinsey, J. C.; Geohegan, W. A., and Aidar, O. J.: Functional Reorganization of Sympathetic Ganglia Following Preganglionectomy, Tr. Am. Neurol. A. **68**:45, 1942.

follow, with reinnervation of postganglionic fibers through the first thoracic segment. If this mechanism operates in man, the preganglionic sympathectomy for the arm might be followed by recurrence through the stellate ganglion.

Epinephrine in small amounts augments the transmission of impulses in sympathetic ganglions but in large amounts depresses it. In clinical shock, a sudden liberation of large quantities of epinephrine may produce a depression.[175]

The importance of removing the ganglion opposite the second lumbar vertebra is emphasized by Atlas.[176] There is no standard arrangement of ganglions, and this way the most important segment is excised.

Shumacker [177] reports a sympathetic denervation of 83 extremities and discusses indication, technic and results, which are in perfect accord with present opinion on this subject. He also reports a good result following lumbar sympathectomy for livedo reticularis. The mottling still remained but became pink. In our experience with a recent case, the dry, warm extremity does not satisfy the patient when the mottling persists, since the cosmetic result is not perfect.

An interesting observation led Shumacker to try lumbar sympathetic block to anesthetize uterine contractions, since the patient with livedo reticularis had a completely painless labor.

Abramson and others [178] investigated the blood flow in poliomyelitic limbs and found that it was not reduced. His argument that such patients should not be subjected to sympathectomy may not hold for all cases, since in a definite group of children the reaction of the paralyzed limb to cold is exaggerated and the swollen plum-colored extremities are benefited by sympathectomy.

THE SURGICAL TREATMENT OF HYPERTENSION

The only denervations which produced marked hypersensitivity of the intestinal smooth muscle to epinephrine were found to be those which involved sectioning of the axons passing to the intestines from cell bodies located in the preaortic ganglions.[179] This study confirms the wisdom of cutting splanchnic nerves and lumbar chains for hypertension without injury or excision of the preaortic ganglions. Certainly the clinical disturbances of the gastrointestinal tract after section of the splanchnic nerve are slight compared with those occurring after celiac ganglionectomy, an operation not to be recommended.

A common cause of hydronephrosis in early life is the aberrant renal vessel.[180] It was noted in 0.375 per cent of the autopsies on patients below the age of 12 years. In children simple ligation of such a vessel is better tolerated than in adults, who may need a partial resection of the kidney.

In 5 patients suffering from essential hypertension, renal blood flow was studied before and after sympathectomy. No important changes were noted. The

175. Bülbring, E., and Burn, J. H.: Action of Adrenaline on Transmission in Sympathetic Ganglia, Which May Play a Part in Shock, J. Physiol. **101**:289 (Nov. 30) 1942.

176. Atlas, L. N.: Sympathetic Denervation Limited to the Blood Vessels of the Leg and Foot, Ann. Surg. **116**:476 (Sept.) 1942.

177. Shumacker, H. B., Jr.: Sympathectomy in the Treatment of Peripheral Vascular Disease, Surgery **13**:1 (Jan.) 1943.

178. Abramson, D. I.; Flachs, K.; Freiberg, J. A., and Mirsky, I. A.: Blood Flow in Extremities Affected by Anterior Poliomyelitis, Arch. Int. Med. **71**:391 (March) 1943.

179. Youmans, W. B.; Karstens, A. I., and Aumann, K. W.: Effect of Vagotomy and Sympathectomy on Sensitivity of Intestinal Smooth Muscle to Adrenalin, Am. J. Physiol. **137**:87 (Aug.) 1942.

180. White, R. R., and Wyatt, G. M.: Surgical Importance of Aberrant Renal Vessel in Infants and Children, Am. J. Surg. **58**:48 (Oct.) 1942.

cases presented, however, were such that a flexibility of the renal vascular bed could hardly be expected.[181]

Bordley, Galdston and Dandy[182] followed 10 patients from three to seven years after sympathectomy for hypertension—a truly admirable follow-up. Two patients died shortly after operation. Three supradiaphragmatic and 7 infradiaphragmatic operations were done. The sole criterion for operating was the presence of incapacitating symptoms. Relief of symptoms occurred. Postural hypotension was absent in the patients who had supradiaphragmatic operations but present in 4 of the 7 who had infradiaphragmatic ones. In none of the patients was sexual function impaired. The responses to the cold pressor and the sodium amytal test did not change postoperatively. One of the patients who underwent a supradiaphragmatic operation had a good reduction of blood pressure for four and a half years and then had a return to the preoperative level for the two and a half years preceding the report. Postural dyspnea occurred with postural hypotension; this has not been reported before. The best case was that of a 29 year old woman with a hypertension of very short duration.

It is our impression that with a more extended, complete splanchnic section and with a group of patients seen in an earlier stage the results are still better. This is certainly the best postoperative study that has been so far reported.

A group of 54 cases is reported from the Lahey clinic by Bartels, Poppen and Richards.[183] Their indications have gradually changed with increasing experience. The blood pressure must fall to 150 systolic and 100 diastolic while the patient is at rest and under sedation. Of the patients with grade II hypertension 55 per cent obtained a drop in pressure; of those with grade III hypertension 37 per cent were benefited. Of 20 patients more than 40 years old only 2 obtained relief, whereas of 32 patients less than 40 years old 68 per cent had a drop in blood pressure. No persons with grade IV hypertension were subjected to an operation in the more recent series. Four patients had normal kidneys revealed by biopsy; they all obtained clinical relief. It is obvious from this study that surgical treatment of hypertension will have to be urged for persons with much earlier stages, preferably for persons with the asymptomatic forms which are recognized on insurance or preemployment examinations.

AMPUTATIONS

Thorek[184] advocates a flapless amputation of the thigh without a tourniquet. He is against the use of spinal anesthesia, because it increases the incidence of thrombosis; he advocates suture of the fascia lata, uses no drainage and injects alcohol into the nerve stump.

Theis[185] reports on 50 amputations for advanced arterial disease; he believes that his mortality is as low as has been recorded in spite of intensive efforts to save the limbs by conservative measures. He has seen aggravation of infection by suction and pressure treatment, by closing the stump in the presence of spread-

181. Findley, T.; Clinton E., and Edwards, J. C.: The Effect of Sympathectomy on Renal Blood Flow in Essential Hypertension, Surgery **12**:64 (July) 1942.

182. Bordley, J.; Galdston, M., and Dandy, W. H.: The Treatment of Essential Hypertension by Sympathectomy: A Report on Twelve Patients Three to Seven Years Following Operation, Bull. Johns Hopkins Hosp. **72**:127 (March) 1943.

183. Bartels, E. C.; Poppen, J. L., and Richards, R. L.: Surgical Treatment of Hypertension: Results in Fifty-Four Cases, Ann. Int. Med. **17**:807 (Nov.) 1942.

184. Thorek, P.: A Simplified Technique for Thigh Amputation, Surg., Gynec. & Obst. **75**:225 (Aug.) 1942.

185. Theis, F. V.: Amputations for Advanced Arterial Disease, Surg., Gynec. & Obst. **76**:35 (Jan.) 1943.

ing infection and by local amputation of toes. The author emphasizes the use of the oscillometer but does not use histamine flares for determination of the level of amputation.

McLaughlin [186] recommends pentothal sodium for minor surgical procedures and low spinal anesthesia, with 50 mg. of procaine hydrochloride, for major amputations in persons with diabetes. If inhalation anesthesia is necessary, he prefers cyclopropane. In the presence of severe infection, a two stage procedure is employed; the use of drains is advisable in most cases. The two stage procedure and the local use of sulfanilamide will decrease the need for drainage. Follow-up studies revealed that approximately 50 per cent of the patients who had an amputation were dead within one year after discharge from the hospital.

Refrigeration of limbs to prevent absorption of toxins and advance of bacterial infection and to relieve pain prior and during amputation is discussed by McElvenny.[187] Chief pharmacist's mate Kennedy [188] describes a simple ice container for use in amputations.

The reviewed five articles on amputations contain many controversial points. The experiences of the present war may clarify many points. The tendency toward simple procedures, effective safe anesthetic methods and close control of infection is unmistakable. The late sequelae of amputations, phantom limbs and causalgic states, are most stimulatingly discussed in a monograph by Livingston.[189]

LIGATION OF THE PATENT DUCTUS ARTERIOSUS

Keys and Shapiro [190] have most enlightening data on 57 adults who had postmortem evidence of a patent ductus arteriosus. Forty per cent of these died of subacute bacterial endocarditis and 28 per cent of congestive heart failure; 2 patients died of ruptured aneurysm of the pulmonary artery. Inoperable conditions existed in about 17 per cent of the patients. In the adult the ductus is often very short.

The authors have records on 137 operations, nearly half of which have not been published. In 104 of these there was no infection. Thirty-three patients had subacute bacterial endocarditis. Six patients died of hemorrhage during or following operation. The total surgical mortality was less than 10 per cent. A rough calculation would suggest that there are about 20,000 persons in the United States suffering from this anomaly. Attempt at ligation is justifiable in spite of the fact that the patient's circulation seems well adjusted at the time; but it must be expected that difficult or impossible conditions may be encountered.

In a number of articles, Touroff [191] continues his remarkable reports on the closure of the patent ductus in the presence of subacute bacterial endocarditis. He has now done 12 operations, with 7 recoveries, 3 failures and 2 surgical deaths. He points out that in the early stages of infection the vegetations are confined to the

186. McLaughlin, C. W., Jr.: The Surgical Management of Diabetic Gangrene, Surgery **13**:423 (March) 1943.

187. McElvenny, R. T.: The Present Status of Cooling Limbs in Preparation for Surgical Procedures, Am. J. Surg. **58**:110 (Oct.) 1942.

188. Kennedy, J. A.: A Technic and Device for Application of Ice Anesthesia for Amputation of Extremities, U. S. Nav. M. Bull. **41**:226 (Jan.) 1943.

189. Livingston, W. K.: Pain Mechanisms: A Physiologic Interpretation of Causalgia and Its Related States, New York, The Macmillan Company, 1943.

190. Keys, A., and Shapiro, M. J.: Patency of the Ductus Arteriosus in Adults, Am. Heart J. **25**:158 (Feb.) 1943.

191. Touroff, A. S. W.: Further Experiences in the Surgical Treatment of Subacute Streptococcus Viridans Endocarditis Superimposed on Patent Ductus Arteriosus, J. Thoracic Surg. **12**:1 (Oct.) 1942; The Results of Surgical Treatment of Patency of the Ductus Arteriosus Complicated by Subacute Bacterial Endocarditis, Am. Heart J. **25**:187 (Feb.) 1943.

ductus and the pulmonary artery; later they may spread to the cardiac valves or to the aorta. Aortic involvement is favored by a short duct. When peripheral emboli have occurred or when other congenital anomalies are present elsewhere, the ligation is not indicated.

The chief dangers of the operations are hemorrhage and injury to the left recurrent laryngeal nerve. In the presence of subacute bacterial endocarditis the likelihood of accidental hemorrhage is increased, because of the friability of the duct. The authors make several technical suggestions, which have resulted in freedom from this complication in the last 4 cases; also the time of operation may be materially reduced.

Other cases are reported by Nixon [192] and O'Connell.[193] It seems that pediatricians and cardiologists should seriously consider the single uninfected patent ductus arteriosus as a surgical indication. Gross has now performed 30 operations, with 2 deaths; Jones, 26, with 2 deaths. These were in cases without infection; obviously the presence of the bacterial endocarditis increases the risk, but, as Touroff has demonstrated, even in such cases there is a chance for cure.

In a recent report on 6 patients made by Harrington,[194] 1 had subacute bacterial endocarditis. This 15 year old girl made a dramatic recovery. Harrington has devised a posterior approach through resection of the fourth rib, which seems to have much in its favor.

It is my impression that ligation of the patent ductus arteriosus is one of the most significant advances in vascular surgery.

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192. Nixon, J. W.: Ligation of a Patent Ductus Arteriosus: Report of a Successful Case, Surgery **12**:31 (July) 1942.

193. O'Connell, W. S.: Ligation of a Patent Ductus Arteriosus, Taft's M. J. **8**:101 1942.

194. Harrington, S. W.: Patent Ductus Arteriosus with Bacterial Endocarditis: Transpleural Ligation Through Posterolateral Approach; Report of Case, Proc. Staff Meet., Mayo Clin. **18**:217 (July 14) 1943.

Book Reviews

Behavior and Neurosis. By Jules H. Masserman, M.D. Price, $3.00. Pp. 269. Chicago: The University of Chicago Press, 1943.

Dr. Masserman has done a thorough and workman-like job. This is true both of his experimentation and of his study of the various interrelated fields with which his experimentation is concerned. His theoretic approach to the problem—the experimental induction and reduction of "neuroses" in cats—is holistic, and he is at great pains to refute the mechanistic concepts of the representatives of the Pavlovian and the post-Pavlovian school of thought. They, he says, are guilty of entangling themselves in an ever increasing complexity of terminology in an effort to uphold a position which can be more easily and coherently explained by assuming: "(a) that behavior is motivated by the needs of the organism; (b) behavior is reactively attuned to the animal's interpretation of the physical and social meanings of its environment; and (c) that instinctual satisfaction and adaptation may be supplemented even in animals by expressive, substitutive, or symbolic conduct," (p. 13). This view is held by both the modern and the eclectic school of biologic thought as well as by the psychoanalysts.

He demonstrates that the hypothalamus is not a locus of sensory or affective emotionality but simply a coordinating motor station, stimulation of which produces no meaningful experience for the animal. He observes that frustration alone rarely brings forth neurotic symptoms but that it is necessary to have conflict of two opposing affects.

The therapeutic methods and their relative efficiency are interesting. The most effective method is "working through"; i. e., the animal by being given opportunity to manipulate the conflictful situation plus encouragement from the experimenter gradually overcomes the neurosis and the fear of the situation producing it.

Synopsis of Diseases of the Skin. By Richard L. Sutton, M.D., and Richard L. Sutton Jr., M.D. Price, $5.50. Pp. 481. St. Louis: C. V. Mosby Company, 1942.

The Suttons, *père et fils,* have collaborated to present in a compact form a general discussion of diseases of the skin. The material is prepared primarily for the physician in general practice rather than for the specialist in dermatology. In order best to use their space, the authors have concentrated on simplicity and condensation; so they devote most of the space to common conditions and allot only a little to unusual ones. To further enhance the essentially practical quality of the book there is an illustration on nearly every page. The illustrations are well selected and for the most part are clearcut and readily interpreted. One minor criticism of the book has to do with the presentation of the systemic diseases which have cutaneous manifestations. One tends to gain the impression that the cutaneous lesions are of primary importance, whereas actually the underlying etiologic factor should dominate the whole consideration of the disease. The book can be highly approved and is recommended to practitioners of medicine who see patients with cutaneous disorders only from time to time.

Kaiser Wakes the Doctors. By Paul de Kruif. Price $2.00. Pp. 158. New York: Harcourt, Brace and Company, 1943.

Paul de Kruif always writes cleverly and with enviable facility. Here he calls himself a medical reporter, telling in journalistic fashion the story of the medical organization of Mr. Henry J. Kaiser's ship-building projects.

The book begins with an account of Dr. Sidney Garfield's twelve bed hospital in Desert Center and shows how the idea back of this—a hospital supported by many small contributions from well persons to insure good care when illness finally comes—was developed later by Mr. Kaiser at Grand Coulee and Permanente, and finally on a still larger scale to include 125,000 workers and their families of the shipyards in Richmond, Oakland and Vancouver, Washington.

Obviously, in Dr. de Kruif's opinion, Mr. Kaiser has managed to finance the cost of good medical care successfully, and obviously, too, Dr. de Kruif has been much impressed by Mr. Kaiser. He believes that Mr. Kaiser's methods, adopted to meet a wartime medical emergency, will prove sufficiently durable to carry over into times of peace. Thus he ends with the generality that some form of public health and hospital insurance will come into its own after the war because in all probability the structure of medicine can no longer be supported by charity, by endowments or by large grants of money from a few sources. This will be all right if only a man like Mr. Kaiser continues to spur on the doctors and keep them awake.

The book is written for the general public rather than for the members of the medical profession. It seems to have been put together in a hurry and reads almost as if it had been dictated, so that its literary style is affectedly colloquial. But it is a short volume and easily read.

Hypertension. By Irvine H. Page, M.D. Price $1.50. Pp. 80, with 7 illustrations. Springfield, Ill.: Charles C Thomas, Publisher, 1943.

"The person who is suddenly told he has high blood pressure is frightened and bewildered." With this first sentence the reviewer parts company with the author. Doctors should not tell patients about blood pressure in such a way as to frighten and bewilder them; they must go to great pains to accomplish the opposite of this. If they fail, the situation will probably not be remedied by this manual, which may at many points create more alarm: from the picture of the arteriosclerotic vessel to the statement that the damaged arteries may give way, and on to the therapeutic advice which is quite sound but of necessity purely general. The truth of the matter is that the whole idea of manuals of this sort, no matter how well they are prepared, is open to question. For diabetic patients a well devised manual is, to be sure, useful if not actually necessary, because of the mathematical data on diet and on sugar in the urine and blood which must be dealt with. When it comes, however, to hypertension, pernicious anemia, gastric ulcer, allergy, etc., such compendiums in no sense can replace the individual advice which the doctor must give to each patient, a fact which most of the writers themselves take pains to emphasize.

The Epidemiology of Rheumatic Fever and Some of Its Public Health Aspects. By John R. Paul, M.D., and other contributors, for the American Heart Association. New York: Metropolitan Life Insurance Company, 1943.

The author looks on rheumatic fever as a specific disease, though he admits that there is not uniformity of opinion in so regarding it. The argument centers on the relationship of hemolytic streptococcic infections to rheumatic fever. There is no doubt of the close relationship between the two. Nevertheless it has not been proved that hemolytic streptococci are the only infectious agents in rheumatic fever, and until this question has been settled it is wise to consider it a distinct disease.

Rheumatic fever has been poorly defined and has been neglected in compilations of vital statistics. Only a rough estimate of its incidence and importance can be obtained. However, in the northern half of the country it probably ranks next to tuberculosis and syphilis among the chronic infections.

The period of greatest susceptibility is that of midchildhood, which is due in part perhaps to the fact that there is more opportunity for exposure at this age.

Both environment and inherited tendencies are important in determining the prevalence of rheumatic fever. Among environmental factors, climate, season and living conditions are important. The important features in the living conditions seem to be crowding, poverty and perhaps damp living quarters.

A study of rheumatic families has revealed that there is an inherited tendency to acquire the disease.

The author stresses the fact that the public health aspects of rheumatic fever have been neglected. A first step must be education of physicians, nurses and social service workers to the importance of the problem. Main effort should be concentrated on early recognition of the disease and provision of adequate facilities for the care of those who are already suffering from it.

This excellent monograph deserves the attention of all who are interested in rheumatic fever.

Allergy, Anaphylaxis and Immunotherapy. By Bret Ratner, M.D. Price $8.50. Pp. 834. Baltimore: Williams & Wilkins Company, 1943.

The title of this book rather belies its contents. One would gather the impression that it was a book on allergy prepared by an allergist for allergists. On the contrary, the author is clinical professor of pediatrics in one of the New York schools and the book has been prepared for the practitioner of medicine who is engaged in the treatment of disease and all its ramifications. Ratner was motivated, as he says in the preface, by a desire to understand allergy. Then having gained knowledge of this very important physical state, it became obvious to him that it would be wise to acquaint the medical profession with the reasons why serums and vaccines were given, why blood substitutes and sulfonamides were an integral part of chemotherapy and why these various agents acted as they did. It would seem that the author has well accomplished his objective. As a practicing physician he presents a clear exposition of the general principles of immunotherapy and the methods of making use of immuno-

therapeutic agents and to these two main sections he has added an excellent description of the allergic state.

It is rather interesting that there are some forty diseases or disorders which may be treated by vaccines, serums, toxins and other potent biologic preparations. Most of these diseases are considered to a very wide extent so far as their treatment is concerned. A few of the rarer conditions are not elaborated on in quite so much detail. As the section on treatment (immunotherapy) occupies a goodly portion of the book, it can be seen that the work should be of great value to the practicing physician. For this purpose alone it can be recommended without qualification.

The format of the book is excellent. One criticism might be made of the typography, that is, that some of the illustrations are not particularly clear, due either to poor focusing of the camera which made the pictures or else to the grade of paper that is used in the book.

Tifus exantemático: Etiología—clínica—profilaxis. By Prof. Dr. G. Clavero and Dr. F. Pérez Gallardo. Pp. 166 and xvi, with a prologue by Dr. Jose A. Palanca, Director of Health. Madrid: Gráficas Afrodisio Aguado, S. A., 1941.

This monograph is a concise presentation of classic typhus. After a brief sketch of the history and the geographic distribution, in which are presented data on the recent epidemic in Spain, the disease is described in considerable detail. The etiology, clincal characterstics, pathologic anatomy, immunology, epidemiology and prophylaxis are all well outlined. Laboratory procedures useful in the study of the disease are also included. In an appendix several related rickettsial diseases, namely endemic typhus, tabardillo, Rocky Mountain spotted fever and others, are briefly mentioned for the sake of completeness.

The authors note that vaccination with the vaccine prepared by the method of Cox (United States Public Health Service) was tried in Spain. Their impression is that the vaccine did not protect against infection but that it served definitely to ameliorate an attack of the disease.

In a later publication (La prueba intradérmica de Giroud en la infección tifoexantemática, *Rev. San. y hig. pub.*, December 1942) the same authors report their experience with the detection of immune bodies in human serum by means of a cutaneous test on rabbits. When living rickettsias from egg membranes are injected intradermally, a local lesion, consisting of erythema, nodule formation and sometimes central necrosis, appears within forty-eight hours. If the rickettsias are first incubated with immune serum the lesion does not appear. The test continues to give a positive result for at least eleven months after infection.

News and Comment

Dr. Nathan S. Davis III of Chicago Honored.—Dr. Nathan S. Davis III, of Chicago, assistant professor of medicine, Northwestern University Medical School, has been awarded the Distinguished Service Award of the Mississippi Valley Medical Society, consisting of a gold medal and a certificate. The citation in connection with the award reads: "A high type of physician, an able clinician, a very accurate investigator and, last but not least, a writer of syndicated medical advice for the public. While he descends from an illustrious family in medicine, he has carved his own nitch in the profession."